Surgical treatment of secondary glaucoma in non-infectious pediatric uveitis
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CHAPTER 1

General introduction and aims of the thesis
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This thesis concentrates on children with uveitis who develop secondary glaucoma. It combines aspects of three different subspecialties: pediatric ophthalmology, uveitis, and glaucoma. All three subspecialties have their own challenges, new developments, and required expertise. The thesis will focus on risk factors for developing glaucoma and surgical treatment options for glaucoma and their results, in pediatric uveitis patients. In this general introduction, I will introduce the topic and give an overview of developments that have taken place in the past decades to provide a context for the newer data covered in the thesis.
1. PEDIATRIC OPHTHALMOLOGY

Incidence
From a large retrospective dataset of 10,759,066 children (<19 years) from the United States, the prevalence of any significant ophthalmic diagnosis was 6.7%, and thereby relatively common. The most common disease diagnosed was strabismus (3.2%), followed by amblyopia (1.5%) (Pineles et al. 2022). More ophthalmic diseases were diagnosed in higher-income families. This aspect could indicate missed diagnoses in lower-income families, and shows the importance of adequate health care access for diagnosis and subsequent treatment of ophthalmic diseases in children.

Presentation form – description
In children, the diagnosis of an ophthalmic disease may be delayed, because of an asymptomatic presentation and because young children may not complain of a decreased visual acuity. Thus, parents may seek help at a relatively late stage of the disease, when structural changes are visible or when strabismus develops. With delayed diagnosis, the risk of irreversible ocular complications, such as amblyopia, is significant (Campbell and Charney 1991; Koo, Gilbert, and VanderVeen 2017). Therefore, regular examinations after birth at the child health care centre and at school are essential.

Diagnosis
To make the correct diagnosis, children must undergo examinations that can be stressful, or which are difficult to perform. Many adaptations are available for ophthalmic examinations, such as handheld instruments and adapted tests to measure visual acuity by age group (Saxena, Sharma, and Pediatric Ophthalmology Expert Group 2020). To provide optimal pediatric ophthalmic care, close collaboration with orthoptists is essential. Since ophthalmic diseases can be secondary to systemic diseases, additional consultation and/or examination (such as blood tests or imaging) may be indicated, and therefore close cooperation with the pediatric department is important.

General challenges
The age of the patient determines the options for ophthalmic examination and treatment. The lack of cooperation at an early age often requires multiple appointments to perform all necessary examinations. Repetitive examinations and visits to the hospital can lead to mental trauma and delayed development in school (Guerriero et al. 2022). Special knowledge and skills are needed to balance between too many and too few examinations in children. General anesthesia is needed more often in
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children, for examinations and surgical procedures. Treatment must be adjusted, since the risk profile and dosage of a drug may differ depending on age and weight, respectively, and the method of administration may have to be adjusted. For example, in young children, daytime mydriatics may increase the risk of amblyopia and learning disabilities at school due to the loss of accommodation by cycloplegia, and short-acting mydriatics may be preferred (Al-Haddad et al. 2019). As another example, long-term use of systemic medication may create drug intolerance, with a risk of noncompliance.

Another challenge is the lack of presentation of symptoms. Even if a child has reached an age when they can express themselves through language, their recognition of a disease and/or its progression remains difficult. Behavioral changes noted by parents/caregivers are thus of great importance. Children do not pay much attention to difficulties, and report their burdens poorly. For example, studies using quality of life (QoL) questionnaires found a significant negative impact of uveitis on QoL of children, which is more evident when reported by the parents than by the children themselves. These differences could indicate a different frame of reference or parental concern and/or a lack of recognition of the disease and its impact by the child (Sestan et al. 2020).

2. PEDIATRIC UVEITIS

Classification

Uveitis is characterized by inflammation of the iris, choroid and/or retina (Figure 1.1). In 2005, the Standardization of Uveitis Nomenclature (SUN) Working group developed an essential guideline for reporting clinical data in uveitis research, which is also used in clinical practice (Jabs et al. 2005). An anatomical classification of uveitis was made, including anterior uveitis (anterior chamber as primary site of inflammation), intermediate uveitis (vitreous as primary site), posterior uveitis (retina or choroid as primary site) and panuveitis (anterior chamber, vitreous and retina/choroid as primary sites of inflammation). In addition, different types of onset (sudden or insidious), duration (limited or persistent), and course (acute, recurrent or chronic) of uveitis were formulated. A grading scheme of uveitis activity (inactive, worsening activity, improved activity or remission), based on anterior chamber cells and/or vitreous haze grading, was established. Essential complications that should be documented in studies were discussed (which applies to macular edema, formation of epiretinal membrane, neovascularization of the optic disc/retina and glaucoma), including the needed ancillary test for confirmation. Currently, these classifications are still used as standards worldwide (Heiligenhaus, Rothaus, and Pleyer 2021). In 2021, the SUN guidelines were extended with descriptions of various uveitis entities (Heiligenhaus, Rothaus, and Pleyer 2021; Standardization of Uveitis Nomenclature (SUN) Working
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Etiology
Uveitis is a rare disease in the pediatric population (<19 years), with an estimated incidence of 4.3 per 100,000 per year and a prevalence of 27.9 per 100,000 (Zierhut et al. 2005; Päivönsalo-Hietanen, Tuominen, and Saari 2000). The inflammatory reaction can be caused by infection or by an autoimmune response (called non-infectious uveitis). Non-infectious uveitis accounts for 69-95% of pediatric uveitis, and is partly associated with a systemic disease. This thesis focuses on non-infectious uveitis (de Boer, Wulffraat, and Rothova Br 2003; Hettinga et al. 2015).

To diagnose a non-infectious uveitis and thereby excluding an infectious cause as well as possible, a pediatrician consultation is essential. In 41-47% of the non-infectious
uveitis cases, the uveitis is associated with Juvenile Idiopathic Arthritis (JIA), which is thereby the most common systemic disease, related to pediatric uveitis. Less frequently, uveitis is secondary to spondyloarthritis, tubulointerstitial nephritis and uveitis, Blau syndrome, Behcet’s disease and ‘undifferentiated inflammatory disease’ (Cann et al. 2018). In 28–51%, no cause is found (called idiopathic chronic uveitis) (Edelsten et al. 2003; Tugal-Tutkun et al. 1996).

JIA is the most common childhood rheumatic disease and is a collective term for all forms of autoimmune arthritis of unknown etiology that begin before the age of 16 years and persist for >6 weeks (Ravelli et al. 2005). Seven subgroups are formulated, based on the number of joints involved, presence/absence of specific immune related factors (rheumatoid factor/ antinuclear antibody (ANA)/ Human Leukocyte Antigens (HLA)-B27) and other symptoms, like skin involvement (Minden and Niewerth 2008). In addition to previously mentioned autoimmune factors, JIA phenotype is influenced by the genetic profile and environmental factors and infections (Prahalad and Glass 2008). However, the specific pathogenesis of JIA-associated uveitis (JIA-U) is not understood, nor has the relationship between the eye and the joint inflammation been established. Particular subtypes of JIA are especially associated with uveitis: oligoarthritis (involvement of < 5 joints), polyarticular rheumatoid factor negative (involvement of > 4 joints), and psoriatic subtypes (skin involvement). Associated phenotypic features are asymmetric arthritis, an early age of onset, female predisposition and antinuclear antibody (ANA) positivity (Kalinina Ayuso et al. 2014).

There are substantial variations in the geographic and ethnic distribution of non-infectious uveitis etiologies in children and thereby also the type of uveitis (Tugal-Tutkun 2011). As for JIA-U, JIA is the leading cause of anterior uveitis in series reported from Northern European countries and from the USA, whereas it is less frequent in Mediterranean and Middle Eastern countries, as well as in India (Tugal-Tutkun 2011). Additionally, the subtypes of JIA differ significantly among different countries (Tanya et al. 2020). For example, there are large regional differences in ANA positivity in JIA patients, with <15% in China, India and Turkey, < 40% in Taiwan, Thailand, the Middle East and the US, and 58–63% in Europe and Canada. Because the different subgroups have their own risk for the development of uveitis and complications, it is important to be aware of these differences.

**Diagnosis**
Overall, non-infectious uveitis is most frequently located anteriorly (75%), and JIA-U is almost always (98%) an anterior uveitis (Cann et al. 2018). The clinical presentation of active uveitis can vary enormously, with HLA B27-associated anterior
uveitis presenting itself with typical symptoms such as limbal hyperemia, pain, and photophobia, whereas in JIA-U, no symptoms may be present at all. The diagnosis of JIA-U can be significantly delayed due to this silent presentation.

Along with the association between JIA and uveitis, in 1990, Kanski et al. suggested for the first time the need for uveitis screening because of the silent presentation of the disease (Kanski 1990). A few years later, the American Academy of Pediatrics developed a guideline for ophthalmic examinations in children with arthritis (Yancey et al. 1993). To promote uniformization of terminologies used for research and guideline development for juvenile arthritis and the associated uveitis, classifications for arthritis were established by the International League Against Rheumatism (ILAR) and the American College of Rheumatology and the European League Against Rheumatism (EULAR) and after coining several names, consensus was finally reached on the term "JIA" to describe the systemic disease (Berntson et al. 2001). As mentioned before, a few years later, ophthalmological standardizations were established by the SUN Working Group (SUN)(Jabs et al. 2005). All the types of uveitis (anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis) have their specific course and risk of complications. It is important to determine the correct type of uveitis with the goal of initiating the most appropriate treatment and follow-up.

General challenges
Non-infectious uveitis in children often has a chronic and complicated course. Due to delayed diagnosis in case of a symptom free presentation, complications may already have occurred. The most common anterior segment complications related to anterior uveitis are cataract (clouding of the normally clear lens), band keratopathy (calcification of the cornea), and glaucoma (damage of the optic disc, whereas other complications include cystoid macular edema (edema in the center of the retina) and papillitis (optic nerve inflammation)(de Boer, Wulffraat, and Rothova Br 2003).

Visual impairment is common in pediatric non-infectious uveitis. In 2018, Cann et al. reported a unilateral visual acuity of > 0.3 Logarithm of the Minimum Angle of Resolution (LogMAR) in 0.05/Eye Year and ≥ 1.0 LogMAR in 0.01/Eye Year (using a scale from 0 to 1 LogMAR, in which 0 LogMAR means 100% visual acuity (a.k.a. 6/6 Snellen visual acuity) and 1 LogMAR means 10% visual acuity (a.k.a. 6/60 Snellen visual acuity)(Cann et al. 2018). The most common and significant risk factor for a decrease in the visual acuity was the presence of posterior synechiae at diagnosis. Other complications at diagnosis, leading to significant vision loss, were cataract, raised intraocular pressure (IOP), papillitis, band keratopathy, macula edema, hypotony (IOP below normal) and an epiretinal membrane.
3. PEDIATRIC UVEITIC GLAUCOMA

Background
‘Elevated IOP’, ‘ocular hypertension’, and ‘glaucoma’ are all terms describing different aspects of an increase in IOP. Glaucoma is defined as optic nerve damage, most often due to a high IOP. Damage of the optic nerve results in visual field loss and may eventually cause blindness. Lowering the IOP is intended to limit the damage of the optic disc.

Because different terms can be used, the SUN working group defined terms for uveitic glaucoma. The term elevated IOP should be used for those situations, when IOP rises above a defined normal range. The threshold for considering a rise in IOP substantial (for example, as in a rise in IOP attributable to the use of topical steroids) was set at a rise of 10 mmHg or more as compared to baseline IOP. One option for describing an IOP above normal range is to report at two levels: above 21 mmHg (the traditional “upper limit of normal”) and above 30 mmHg (a level above which many practitioners would initiate treatment even without evidence of glaucomatous damage). The second option is to report IOP above 24 mmHg as elevated, since the risk of glaucoma seems to increase substantially as IOP rises above this level (Jabs et al. 2005; Sommer et al. 1991). In this thesis, I used the traditional “upper limit of normal” cutoff values.

The increase in IOP is the result of a disbalance of the production of aqueous humor by the ciliary body and the outflow of the aqueous humor through the trabecular meshwork (the conventional outflow pathway) and the uveoscleral pathways, all located in the anterior chamber angle (Figure 1.2 and Figure 1.3). The former accounts for 70-95% of the aqueous humor outflow and is thereby the most important one.

Multiple mechanisms can cause an increase of IOP. The decrease in aqueous humor outflow may be due to an increased density of the trabecular meshwork by inflammatory cells and/or debris. Also a steroid induced IOP increase can develop and is known to be frequent, severe, and rapid in children (Kaur, Kaushik, and Singh Pandav 2013; Ng et al. 2000; Al Hanaineh et al. 2018). Steroids cause increased production and decreased destruction of the extracellular matrix of the trabecular meshwork. There is an increased deposition of glycosaminoglycans, fibronectin, elastin, and collagen, and reduced activity of matrix metalloproteinases. Both reactions result in increased aqueous outflow resistance (Feroze and Khazaeni 2022). In addition, the outflow of the aqueous humor may be blocked by the formation of iris adhesion to the angle of the anterior chamber (peripheral anterior synechiae), or the aqueous humor flow may be blocked by iris adhesion against the anterior lens capsule (posterior synechiae (Figure 2.2)(resulting in an iris bombans)).
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Figure 1.2 Schematic diagram illustrating the trabecular meshwork conventional outflow pathway. Aqueous humor is produced by the ciliary body and it flows (dashed line shown with arrowheads) from the posterior chamber through the pupil into the anterior chamber. From there it flows out through the trabecular meshwork into the Schlemm's canal and subsequently absorbed into the episcleral veins via the collector channels (from Goel et al. 2010, (creativecommons.org/licenses/by-nc/3.0/)).

Figure 1.3 Schematic diagram illustrating the uveoscleral outflow pathway. Aqueous humor is produced by the ciliary body, in uveoscleral route, it flows from the posterior chamber through the pupil into the anterior chamber and then (shown by dashed lines and arrowheads) through the face of the ciliary body and iris root to the ciliary muscle and suprachoroidal space to either veins in the choroid and sclera or through scleral pores to episcleral tissue (from Goel et al. 2010, (creativecommons.org/licenses/by-nc/3.0/)).
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In chronic uveitis, obstruction of aqueous humor outflow may result from scarring and obliteration of the trabecular meshwork and/or Schlemm’s canal or from overgrowth of a fibrovascular membrane in the anterior chamber angle (Boyle, Netland, and Salim 2008). Neovascularizations may play a role in the development of this membrane (Baquet-Walscheid et al. 2022). Because the trabecular meshwork is the most pronounced area of impact, an uveitis reaction in the anterior chamber is an important risk factor for developing an IOP increase.

Incidence

Previous studies reported an elevated IOP in as many as 2/3rds of all patients with pediatric uveitis within the first 2 years after the diagnosis. The incidence of glaucoma was much lower. Secondary glaucoma developed in 26-30% of patients with pediatric uveitis, at a mean age of 9 years, with the majority of cases developing glaucoma later during follow-up (9% present at diagnosis versus 30% during the follow-up period) (Gautam Seth et al. 2018; 2021).

Secondary glaucoma develops more frequently in JIA-U (38%) compared to other forms of uveitis (11%). Within the JIA subgroups, ANA positive (42%) children are more likely to develop secondary glaucoma, as compared to ANA negative (6%) children (Sijssens et al. 2006).

Diagnosis

The publication of de Boer et al. raised awareness of the need of regular check-ups of the IOP and early treatment of significant rises in IOP in order to prevent blindness due to uveitic glaucoma (de Boer, Wulffraat, and Rothova Br 2003). Together with the formulated definitions of uveitic glaucoma by the SUN working group, ocular hypertension and glaucoma are nowadays recognized at an earlier stage. Techniques to measure the IOP in children and treatment options have also improved.

The oldest technique to measure the IOP is via tactile tension by digital pressure on the globe. However, this method is only moderately reliable and it is difficult to compare measurements at different time points. Von Graefe developed the first instrument for measuring the IOP in 1865. In the late 19th century, Fick, Maklakoff, Priestley Smith, and others engineered numerous tonometers. But while some of these instruments registered the IOP pretty accurately, none of them has ever come into general use either because of their complicated construction or because the measurement required too much time (Marple 1910). The first usable instrument was the Schiøtz tonometer (1905), which used corneal indentation to measure the IOP in a supine position. A calibration scale for the Schiøtz tonometer was formulated in 1909, with updates based
on multiple measurements in 1924, 1948, and 1954 by Friedenwald and Grant. The '1954 scale' was calibrated for the Schiotz, the newer Gradle-Schiotz and the McLean tonometers, and was published by the 'Committee on Standardization of the American Academy of Ophthalmology and Otolaryngology' (The Committee on Standardization of the American Academy of Ophthalmology and Otolaryngology 1955).

With the introduction of Goldmann’s applanation tonometry in 1950 began the era of truly accurate IOP measurement, based on the Imbert-Fick law from the 1800s (Stamper 2011). The measurement must be performed in a seated position, using the slit lamp. Fifteen years later, a handheld version was developed by Perkins, using the same technique (Perkins 1965). Unfortunately, the Perkins applanation tonometer requires a high level of skill to operate and it is less stable than the Goldmann tonometer, due to the handheld aspect (Bader, Zeppieri, and Havens 2022).

The Mackay-Marg tonometer was introduced in 1959, with the Tono-pen (Reichert Ophthalmic Instruments) as its newer format. This technique is a combination of the applanation and indentation process. The Tono-pen is a handheld portable device and can be used in any position. Later, around 1985, pneumotonometry was developed (Guildford and O’Day 1985). This technique also combines applanation and indentation, using a compartment filled with air inside the instrument to measure the pressure required to flatten the cornea using a silicone tip. However, the clinical utility of this type of tonometry remains debatable, as studies have shown that IOP values are generally overestimated (De Moraes et al. 2008).

Non-contact tonometers, which first came available in the 1970s, are also known as ‘air-puff’ tonometry. These instruments use a small puff of air to applanate the central cornea. A puff of air produces a corneal deformity, which is detected as a difference in the ability of the cornea to reflect a beam of light to a reference point (Alguire 1990). The technique for IOP measurement is very useful for IOP screening, because it is easy to perform and no topical anesthesia is needed. However, the measurements are less precise, so the technique cannot be applied for diagnostics or follow-up (Bader, Zeppieri, and Havens 2022; Farhood 2012). The dynamic contour tonometry was developed in 2003 and calculates IOP based on the Pascal principle. The practical implementation of the measurement is at least as difficult, and the results are not superior to Goldmann’s applanation tonometry (Sales-Sanz et al. 2018).

Apart from the non-contact tonometers, all other tonometers need topical anesthesia and adequate cooperation of the patients. In younger children, these measurements often cannot be performed without general anesthesia. Measurement of IOP under
general anesthesia is far from ideal, because it is difficult to organize, making multiple measurements for follow-up impossible. In addition, the influence of the general anesthesia itself causes a reduction of the IOP (Raw and Mostafa 2001).

In 2006, the ICare (Tiolat Oy, Helsinki) was introduced as a portable rebound tonometry, based on the dynamic tonometry principle (Dekking and Coster 1967; Brusini et al. 2006) (Figure 1.4). It utilizes a small disposable probe (composed of a tiny plastic round tip on a thin steel wire) that bounces off the cornea in the horizontal plane. The ICare rebound tonometry is easy to use (handheld), patient-friendly (no topical anesthesia needed), and gives an adequately reliable measurement. This development has made low-threshold measurement of IOP a lot easier in clinical practice especially in children, thus making it possible to diagnose IOP rises at an early stage (Flemmons et al. 2011). The HOME version can be used autonomously for at-home use in managing glaucoma patients (Rosenfeld et al. 2021). New developments include continuous IOP monitoring via contact lenses or implantable IOP-sensor devices (Mansouri and Gillmann 2020; Mariacher et al. 2016). However, these new techniques are still in their infancy, and are not primarily of interest to use in children, because the measurement methods are still far too intensive and/or sensitive.

Figure 1.4 The Icare is user-friendly for eye pressure measurements in children (Onspotmedical.nl)

General challenges
Damage of the optic nerve can be detected by various techniques: by fundoscopy, analyzing the excavation of the optic disc (quantified as cup-to-disc ratio, where with glaucomatous damage the proportion of the cup increases (Figure 1.5)), by perimetry
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(evaluation of visual fields), or by optical coherence tomography (OCT). In children, all these tests have serious limitations.

The fundoscopic evaluation of the optic disc is of moderate reliability, because it can be difficult to perform in a young patient (Strouthidis and Papadopoulos 2013). Additionally, the excavation of the optic disc of a young patient has the capability to reform, when the IOP normalizes, and papillitis can mask glaucomatous damage of the disc (Strouthidis and Papadopoulos 2013; Wu et al. 2002).

![Diagram of optic disc with normal cup and increased cup caused by glaucoma]

**Figure 1.5** Optic disc with normal cup and increased cup caused by glaucoma: (A,B) show optic discs with normal cup and dimension quotes; (C,D) show optic discs with increased cup derived from glaucoma (from Barros et al. 2020, [creativecommons.org/publicdomain/zero/1.0/]).

In adults, perimetry is essential for diagnosing glaucoma (‘European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition’ 2021). The standard visual field examination is time-consuming and a precision work, requiring patience and
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concentration. For this reason, different types of perimetry have been developed for pediatric patients, partly using eye tracking technology (Satgunam et al. 2017; Perperidis et al. 2021). However, none of these tests are routinely used in daily practice, due to the lack of repeatable results or due to the lack of feasibility. Because of this, perimetry does not have a major role in pediatric ophthalmology today.

In adults, OCT evaluation of the retinal nerve fiber layer and/or the macular ganglion cell layer can be used for glaucoma screening, based on a normative database. Unfortunately, there is little information on how to observe the development and progression of optic disc changes in children with the OCT technique, nor is a normative database for this age group available. Moreover, aspects such as papillitis, epiretinal membrane and dense vitreous opacities may distort the results in uveitis patients, making the OCT scans difficult to interpret. In pediatric patients, repeatedly performing OCT scans within the same individual could provide some useful information on changes in the optic disc over a certain time period.

The above described difficulties in the glaucoma diagnosis in pediatric uveitis patients resulted in the recommendation that the diagnosis of secondary glaucoma and the indication for glaucoma surgery in children should be made primarily on the basis of IOP measurements (Kalogeropoulos and Sung 2018; Clement, Bhartiya, and Shaarawy 2014; Shen et al. 2023; Bhola 2022).

4. CLINICAL COURSE OF PEDIATRIC UVEITIC GLAUCOMA

Usually, IOP varies in the course of pediatric uveitis (Gautam Seth et al. 2021). In the active uveitis phase, intraocular pressure is low to normal and it rises at the time point that quiescent uveitis is reached (Kalogeropoulos and Sung 2018). This could reflect a restored function of the ciliary body in combination with an altered trabecular outflow system. Since steroids are often used in the early treatment stages of uveitis, this coincides with a possible steroid response (Kaur, Kaushik, and Singh Pandav 2013; Ng et al. 2000). Often, topical IOP-lowering medication is sufficiently effective to reduce IOP and an IOP plateau phase is reached. However, at later time points, a slow IOP rise may be observed due to irreversible obstruction of aqueous outflow resulting from scarring and obliteration of trabecular meshwork beams/Schlemm’s canal or from overgrowth of a fibrovascular membrane in the chamber angle (Boyle, Netland, and Salim 2008). The affected eye usually becomes unbalanced quite suddenly with a substantial IOP increase, which is then difficult to control with medication alone.
Anti-inflammatory medication
The specific pathogenesis of JIA-U and idiopathic chronic anterior uveitis is not understood, whereas a variety of immune cell subtypes may play a role in the underlying mechanisms. Patients with JIA-U were found to have activated monocytes and distinct T-cell subsets when immune profiling was performed (Walscheid et al. 2019; 2018). Additionally, several studies have shown that B-cells play an important role in JIA-U. The finding of shared genetic risk alleles for both JIA-U and idiopathic chronic anterior uveitis (HLA-DQB1*04:02 and HLA-DRB1*08:01), leads to the hypothesis that the pathogenesis of the different forms of pediatric non-infectious uveitis is similar (Wennink, de Boer, et al. 2021).

In non-infectious pediatric uveitis with a chronic course, long-term anti-inflammatory treatment is indicated, as suboptimal treatment can lead to complications and blindness (Tugal-Tutkun et al. 1996; Rothova et al. 1996; Foster and Rashid 2003). The introduction of steroids in the 1950s for the treatment of ocular inflammation brought a vast improvement in treatment, thanks to their effective and rapid action and the possibility of administering them in different ways (intravenous, oral, and topical (eye drops, peribulbar or intravitreal injections or intravitreal implants) (Gordon 1956). In spite of these advantages, the risk profile of steroids may be serious, especially in children (Oray et al. 2016). Therefore, treatment regimens in pediatric uveitis aim for only short-term use of high doses of systemic or local steroids. For long-term treatment, systemic non-steroid immune modulating drugs are used and steroid eye drops are used at a low frequency of maximally 2 to 3 times a day (Lee and Foster 2010; Thorne et al. 2010; Constantin et al. 2018; Quartier 2021).

Systemic treatment with steroids is effective in pediatric uveitis, but with significant side effects such as weight gain, diabetes mellitus, systemic hypertension and developmental delay. When the first types of conventional systemic disease-modifying antirheumatic drugs (csDMARD) were introduced, cyclosporine added tremendous value alongside steroids. Around 2000, methotrexate and mycophenolate mofetil were introduced, with hopeful results and a better safety profile, compared to the side effects of cyclosporine (mainly the nephrotoxicity and systemic hypertension)(Foeldvari and Wierk 2005; Samson et al. 2001). Methotrexate became the most commonly prescribed immunosuppressive drug in pediatric uveiti, however, in 27-48% of children, inflammation was still not controlled and 20% experienced side effects heil (Samson et al. 2001; Heiligenhaus et al. 2015; G. Simonini et al. 2013; Gangaputra et al. 2009).

If the uveitis remains active with csDMARDs treatment, a biological DMARDs (bDMARDs) is able to suppress the immune system in a more targeted way, with
humanized monoclonal antibodies that inhibit cytokine signaling pathways, including inhibitors of tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6). The first report of results with bDMARDs in pediatric uveitis involved the TNF-alpha inhibitor infliximab in 2005 (Richards et al. 2005). After the SYCAMORE trial demonstrated the efficacy of the TNF-alpha inhibitor adalimumab in combination with methotrexate in JIA, adalimumab was approved by the European Medicines Agency (EMA) for the treatment of non-infectious pediatric anterior uveitis (Ramanan et al. 2017). Adalimumab showed such a clear superiority over placebo (27% treatment failure under adalimumab versus 60% under placebo), that the trial had to be stopped prematurely. The efficacy in JIA-U was confirmed by the randomized French ADJUVITE trial (Quartier et al. 2018). The 2019 ACR guideline for JIA-U recommends the use of TNF-alpha inhibitors, either adalimumab or infliximab (Angeles-Han, Ringold, et al. 2019b).

Humanized monoclonal antibodies directed against the IL-6 receptor (tocilizumab) have been shown to be effective in JIA-U cases where anti-TNF therapy failed due to anti-drug antibodies (Chen, Abiri, and Tsui 2021). Recent studies show encouraging results with the bDMARD IL-6 inhibitor Tocilizumab (especially in persistent cystoid macular edema)(Wennink, Ayuso, et al. 2021). Also, other kinds of bDMARDs are being developed and results are being examined in pediatric uveitis (Maleki et al. 2022). Research trials in JIA-U and ANA-positive anterior uveitis are in process to investigate the effectiveness of Janus Kinase inhibitors as targeted synthetic DMARD (tsDMARD). Positive results in adults with JIA-U were already published in cases-series. A tsDMARD decreases cytokine expression and thereby inhibits inflammation, and might be an option in the future, when csDMARDs and bDMARDs of first choice inadequately suppress the uveitis (El-Shabrawi, Rath, and Heiligenhaus 2022).

Nowadays, with the improved results with DMARDs in a chronic uveitis course in non-infectious uveitis, DMARDs are often used for a longer period of time (> 2 years), with a significant risk of relapse after discontinuation (Kalinina Ayuso et al. 2011; Saboo et al. 2013; Gabriele Simonini et al. 2017; Dick et al. 2018). This development creates friction with the established terminology for activity of uveitis from the SUN classification, whereas clinical remission (inactive disease for ≥3 months with DMARDs) does not correlate with ‘uveitis remission’ according to the SUN classification (inactive disease for ≥3 months after discontinuing all treatment for the ophthalmic disease). In a new era with frequent and prolonged use of DMARDs, a more suitable term should be introduced for these patients, such as “sustained inactivity”, for an inactive uveitis for ≥3 months after discontinuation of all topical anti-inflammatory medication, with the continuation of DMARDs. Unfortunately, due to the lack of the correct term for the
above category of patients, the literature sometimes incorrectly uses “uveitis remission” when assessing the situation independent of the use of anti-inflammatory medication.

**Active versus inactive uveitis – impact on the IOP**
During active uveitis, the ciliary body has a decreased production of aqueous humor, causing a lowering of the IOP. When the uveitis becomes inactive, the ciliary body starts producing the normal amount of aqueous humor. When the trabecular meshwork is damaged and/or has developed a lower potential to provide the outflow of aqueous humor, IOP increases as ciliary body production normalizes.

**IOP increase based on steroid response**
A steroid-induced response is known to be frequent, severe, and rapidly occurring in pediatric uveitis (Kaur, Kaushik, and Singh Pandav 2013; Ng et al. 2000; Al Hanaineh et al. 2018). The elevation of IOP due to steroid use can be found as early as the first or second week of steroid treatment and depends on its dose (Sood and Angeles-Han 2017; Becker and Mills 1963; Carnahan and Goldstein 2000; Kaur et al. 2016). Carnahan et al. conclude that > 2 drops of topical steroids are unwanted, due to a higher chance of intraocular complications (Carnahan and Goldstein 2000).

In the past, topical use of steroids was often the first choice of treatment, but nowadays long-term use and/or high-frequency use of topical steroids is discouraged, because of the high risk of intraocular complications, such as cataracts and glaucoma (Gordon 1956). Early initiation of DMARDs in chronic non-infectious uveitis is therefore advocated to reduce the risk of vision loss (Sen, Dick, and Ramanan 2015; Heiligenhaus et al. 2012).

**Glaucoma and DMARDs**
The clogging of the trabecular meshwork, due to inflammatory cells and debris, is an essential factor for developing an IOP increase. Achieving and maintaining control of intraocular inflammation are key to slow down or maybe prevent the development of uveitic glaucoma. With the ongoing development of new systemic anti-inflammatory agents, pediatric uveitis can be increasingly controlled.

A decrease in the incidence of secondary glaucoma between studies published in 1996 (Tugal-Tutkun et al. 1996), 2003 (Kadayifçilar, Eldem, and Tumer 2003), 2005 (Kump et al. 2005) and 2018 (Cann et al. 2018) may reflect the positive influence of an increasing DMARD use in recent years. Although the rates vary widely, presumably influenced by study groups of different characteristics and a different definition of glaucoma (only 2 of 4 studies distinguished between glaucoma and ocular hypertension), the rate of
secondary glaucoma shows on average a marked decrease. Wennink et al. show the same trend of decrease in glaucoma diagnoses in their cohort with uveitis diagnosis after 2010 in which more bDMARDs are used, compared to their cohort with uveitis diagnosis before 2010 (Wennink et al. 2022). However, the risk of secondary glaucoma remains in children when DMARDs are started later during follow-up. This situation may occur when uveitis is the first presentation of JIA (in 10% of the patients (Sen and Ramanan 2020; Sen, Dick, and Ramanan 2015), in idiopathic chronic uveitis or in patients in countries without systemic JIA screening (Tugal-Tutkun 2011; Ferrara et al. 2019).

5. INTRAOCULAR PRESSURE LOWERING TREATMENT IN PEDIATRIC UVEITIC GLAUCOMA

Pharmaceutical management
The medical treatment of pediatric uveitic glaucoma includes topical β-blockers and topical and systemic carbonic anhydrase inhibitors. However, caution is advised with systemic use of carbonic anhydrase inhibitors, where metabolic acidosis may develop in young children (Capino, Dannaway, and Miller 2016).

Alpha-agonists (especially brimonidine and, to a much lesser extent, apraclonidine) should be administered with considerable caution, especially in children younger than 5 years, due to a risk of central nervous system suppression (eg, sleepiness and cardiorespiratory depression)(Al-Shahwan et al. 2005; Fernandez and Morillo Rojas 2009). Prostaglandin analogues in the setting of uveitis are typically avoided due to concerns about inducing or reactivating inflammation (Parentin 2003; Fechtner et al. 1998; Waheed and Laganowski 2001).

Surgical management
In 59% of pediatric patients with uveitic glaucoma, a surgical intervention is indicated at a mean age of 12 years (Heinz et al. 2009). When planning a procedure for a child with glaucoma, the surgeon needs to consider a strategy that maximizes the control of IOP and preserves vision over decades. The indication for a surgical intervention in pediatric uveitic glaucoma is often not absolute. Most often, children with ongoing substantial IOP rise are initiated for glaucoma surgery, recognizing the risk of a significant reduction in visual acuity due to damage to the optic disc with suboptimal IOP control.

The surgical management of uveitic glaucoma is particularly challenging due to the underlying inflammation. Foster et al. concluded in 2003, based on results after cataract surgery in uveitis patients, that a zero tolerance regime of uveitis activity provides better
outcomes with less surgery related complications (Foster and Rashid 2003). An intense postoperative inflammatory response complicates the control of IOP and uveitis. Although high-dose oral steroids (approximately 1 mg/kg/day) administered preoperatively and in the immediate postoperative period can help suppress this inflammation, glaucoma surgery is most successful when the uveitis is well controlled preoperatively. Together with control of intraocular inflammation, glaucoma surgery can achieve long-term control of IOP and preservation of vision (Bohnsack and Freedman 2013).

Different surgical techniques can achieve a decrease in IOP (Figure 1.6). First, the trabecular meshwork can be incised directly, by which an increased aqueous drainage to Schlemm’s canal can be provided (via goniotomy / trabeculotomy). Second, a decreased aqueous humor production by the ciliary body can be achieved due to its partial destruction with cyclodiode laser (Heinz, Koch, and Heiligenhaus 2006). Third, a new pathway for aqueous drainage can be created from the anterior chamber to the subtenon space (via trabeculectomy / glaucoma drainage implant). Reports regarding the surgical treatment in pediatric uveitic glaucoma were limited, and there was no consensus prior to this thesis on when to use which technique (Papadopoulos et al. 2014).

**Figure 1.6** The different surgical techniques known to be used for pediatric uveitic glaucoma are shown in one image (by author)
6. IMPACT AND VISUAL PROGNOSIS OF PEDIATRIC UVEITIC GLAUCOMA AND ITS TREATMENT

In 1996, Rothova et al. were one of the first to publish about the risk of complications and blindness in non-infectious pediatric uveitis (Rothova et al. 1996). In the same year, Tugal et al. described that 26% of the eyes had a visual acuity of less than 20/200 at the time of first referral to a center of expertise, due to the high rates of complications in these children (Tugal-Tutkun et al. 1996). Frequently seen complications included: cataract (71%), glaucoma (30%), band keratopathy (66%), and hypotony (19%). Patients with JIA had the highest rate of complications and linked to that, they ended up with the lowest final visual acuities. Warned by these numbers in the context of the high prevalence of JIA-U in Western countries, more attention was directed towards the prevention of complications in these children. Medical treatment was optimized (see paragraph on anti-inflammatory medication), surgical interventions were more often performed, techniques became more advanced, and routine IOP checks were implemented in order to better the visual outcomes. In the beginning of the twenty-first century, new data were published. In 2003, de Boer et al. described that, in a study comprising 123 patients, 3 patients (2%) became legally blind and 20 patients (17%) had one legally blind eye caused by uveitis (de Boer, Wulffraat, and Rothova Br 2003). In recent publications, the improving trend in visual acuity appears to continue. Nowadays, with aggressive medical and surgical treatment, visual outcomes are substantially better (Wennink et al. 2022).

The literature shows an impact of pediatric uveitis on the QoL due to increased psychological distress, negative coping strategies, and significant impact on social and professional perspectives (Franke, Schütte, and Heiligenhaus 2005; Böttner et al. 2017). Specific aspects associated with decreased QoL are pain after surgery, lower visual acuity, binocular disease, and three or more surgical procedures (Tupper et al. 2013; Verhagen et al. 2018; Aldarrab et al. 2019). Looking at the above aspects, patients with pediatric uveitic glaucoma requiring surgery are at serious risk for a decrease in QoL.

7. IN SHORT - AIMS OF THE THESIS

The overall aim of the thesis is to gain a better understanding of the development of secondary glaucoma in pediatric uveitis and to compare the outcomes of different surgical treatment options. Because the thesis focuses on a niche area in children, it is difficult to include a large number of study patients. This, in combination with the challenge of combining three areas of expertise (pediatric ophthalmology,
glaucoma, and uveitis) has resulted in only a few publications on this topic in the past. Consequently, clinical practice is largely based on smaller retrospective studies and personal experience. By combining smaller cohort studies for a larger review and a wonderful collaboration with colleagues in Utrecht (the Netherlands), Münster (Germany) and Amsterdam (the Netherlands), knowledge has been pooled in the largest study ever conducted on this topic.

After the previous general introduction of the topic of this thesis, Chapter 2 introduces the most important patient group developing pediatric uveitic glaucoma: JIA-U. This review of JIA-U describes the disease in a broader context, discussing various new developments and insights in the field, covering the following topics: epidemiology, genetics, treatment, risk of developing complications, secondary glaucoma, and chronic anterior uveitis.

Knowledge of risk factors of developing refractory glaucoma requiring a surgical intervention in children with non-infectious uveitis is relevant to the ophthalmologist, in order to organize adequate screening and to properly inform patients and parents. Chapter 3 gives an overview of possible risk factors for a surgical intervention for secondary glaucoma, based on a multicenter, retrospective study. We use the indication for surgery as the main event rather than the diagnosis of ocular hypertension and/or glaucoma so that we can specifically evaluate children with a refractory, and therefore potentially blinding, form of secondary glaucoma.

Chapter 4 is a systematic review of previous research on different types of surgical interventions in secondary glaucoma in pediatric uveitis. Chapter 5 shows the outcomes of a retrospective, multicenter, comparative study of three different surgical protocols in pediatric uveitic glaucoma, focusing on their IOP lowering effect, the reduction in the need of IOP lowering medication, and their success rates. To get an impression of the potential influence on QoL of these protocols, we also analyzed outcomes that are associated with QoL, such as visual acuity, the number of re-interventions under general anesthesia during follow-up, and the length of time after surgery during which failure or re-intervention may occur (representing the time period of uncertainty for patient and parents).

Because uveitis care has undergone a rapid evolution with the advent and acceptance of bDMARDs), Chapter 6 shows the results of a retrospective, multicenter case series on the results of goniotomy as a treatment for pediatric uveitic glaucoma in the newer era of biological treatment. Chapter 7 gives a summary, followed by a general discussion of the thesis, and discusses future perspectives.