CHAPTER

7

Summary and conclusion
Chapter 1 introduces the research topic of the thesis: secondary glaucoma in pediatric uveitis. Three different subspecialties of ophthalmology (pediatric ophthalmology, uveitis, and glaucoma) with their own characteristics, challenges and developments, contribute to this topic.

We discuss aspects of pediatric ophthalmic care that influence our debate the most: the development of the eye and the general physical and mental development of a child. As for the eye, development is still ongoing, with the retina still developing and the optic nerve still subject to reversible changes. The development of amblyopia due to underdevelopment of the retina, is final and should be prevented as much as possible. In addition, when irreversible changes of the optic nerve have developed, lifelong damage control must be performed. Regarding medical treatment in children, it is important to take into consideration that in addition to the known side effects, medical treatment can have specific side effects in children. Also, childhood is an essential period for physical and mental development, and therefore medication can have a significant impact on the child's physical development, quality of life, social development and education (school/friends).

In addition, we introduce pediatric uveitis as a subspecialty in pediatric ophthalmology. Pediatric uveitis is a rare disease in the pediatric population (incidence of 4.3 per 100,000 per year). Of these patients, 2/3rds develop an IOP increase, and 26% develop glaucoma. Because glaucoma is still a blinding disease, a lifelong effective treatment is mandatory. To control the IOP, the treatment and control is often a demanding process for child and parent. For this reason, it is important to optimize the treatment of secondary glaucoma as much as possible. We list past developments and experiences so that we can learn from the knowledge gained, and gather new inspiration for the future.

Chapter 2 displays a review on new developments and insights in the field of pediatric non-infectious uveitis, with a special focus on juvenile idiopathic arthritis (JIA)-related uveitis (van Meerwijk et al. 2023). It covers the following topics: epidemiology, genetics, treatment, risk of developing complications, secondary glaucoma, and idiopathic chronic anterior uveitis. As addressed earlier in Chapter 1, to understand the entire background of the problems and possibilities for patients with JIA-associated uveitis with secondary glaucoma, many different aspects should be considered. By combining recent knowledge and experiences within all the different subgroups, the innovations can help and reinforce each other.
Chapter 3 provides data of a retrospective multicenter study and outlines a risk profile of the need for glaucoma surgery in children with non-infectious uveitis (van Meerwijk et al. 2023). This risk profile helps the clinician to recognize, and thereby treat secondary glaucoma at an early stage. Based on a multivariable analysis, children with JIA-related uveitis had a 1.5-fold higher chance to develop secondary glaucoma as compared to non-JIA uveitis.

The univariable analyses showed a significantly higher IOP during the first uveitis remission and a higher use of topical steroids in eyes that need glaucoma surgery. It is assumable, that topical steroids contribute to the early IOP increase. These observations underscore that efforts should be made to avoid the use of topical steroids as much as possible.

Additionally, our study showed that starting a third type of IOP-lowering medication is a tipping point for needing glaucoma surgery in the near future. Due to the considerable time span of the surgical interventions during the observation period, we emphasize the importance of long-term IOP monitoring and risk assessment.

Chapter 4 provides a literature review of the results of different surgical interventions in pediatric uveitic glaucoma (van Meerwijk, Jansonius, and Los 2022). We included 5 studies about angle surgery (trabeculodialysis, goniotomy, and trabeculotomy), 4 studies about fistulizing procedures (trabeculectomy), 4 studies about glaucoma drainage implant (GDI; Molteno GDI, Ahmed GDI, and Baerveldt GDI), and one study about cyclophotocoagulation.

Looking at their success rates, all these types of glaucoma surgery are able to lower the IOP to an acceptable level during the entire (but often short) follow-up period. However, further optimization is desirable because of the frequent need for revisions and the high complication rates. The wide range of outcomes reflects the huge diversity of the surgical techniques and study designs with very low quality of evidence-grading. It could be concluded that the cyclophotocoagulation procedure has a higher number of re-interventions (due to a very short period of success) compared to the other types of surgical interventions, and is therefore not preferred for secondary glaucoma in pediatric uveitis. Based on the available studies, further differentiations between the other surgical interventions could not be made.

Chapter 5 retrospectively reports on the results of glaucoma surgery in pediatric uveitis in three expert centers. All three centers reached an adequate and significant
decrease in the IOP, without significantly different success rates. The median visual acuity remained stable during follow-up in all three centers.

In addition, we compared the outcomes of a trabeculectomy procedure and a GDI (Ahmed GDI or Baerveldt GDI) and observed that GDIs had higher success rates as compared to trabeculectomy during the entire follow-up. In addition, a lower number of re-interventions related to hypertension were seen in the GDI subgroup.

Our results are in favor of the use of a GDI in pediatric uveitic glaucoma. However, the choice of surgery is multifactorial and should be weighed against the characteristics of the child, the ophthalmic situation (e.g., degree of IOP reduction that is needed), the characteristics of the intervention, and the experience of the surgeon.

**Chapter 6** shows outcomes of a retrospective, two-center study, analyzing the outcomes of a goniotomy procedure as a first intervention in pediatric non-infectious uveitic glaucoma (van Meerwijk et al. 2023). This study indicates that goniotomy might be considered as a primary surgical treatment in these children, because a goniotomy procedure is safe and straightforward, and our results show that it is effective over a follow-up period of 5 years. In most patients, one goniotomy procedure was sufficient, with a success rate of 86% (success was defined as an adequate IOP without major complications or re-interventions). It might be a definite treatment in the majority of eyes, and it can be supplemented by more extensive glaucoma surgery at a later time point if necessary.

**CLINICAL RELEVANCE OF THE THESIS**

Secondary glaucoma in pediatric non-infectious uveitis is a very complex, rare and still potentially blinding disease. Research groups are already focusing on the etiology of JIA and building on this the potential for targeted treatment, which may be the holy grail in preventing intraocular complications in this patient category (Chapter 2). However, idiopathic chronic anterior uveitis will persist unfortunately and thus secondary glaucoma will also remain a potential problem.

In this thesis, we show that blindness can be prevented in most cases with adequate detection of IOP rise and multiple treatment options. Of all the various challenges and issues addressed in this thesis, we want to highlight the most important and clinically relevant aspects.
Surgical technique
None of the surgical interventions for glaucoma described in this thesis were developed specifically for pediatric uveitic glaucoma. Over the years, however, different surgical procedures have been used for these children, and we felt it would be of added value to compare the different surgical interventions as thoroughly as possible, based on the experience already gained. Our review reflects that most experience has been gained with the trabeculectomy and GDI procedures, with preference for a GDI in pseudophakic patients. Based on our research, we would advise a step-wise approach to glaucoma treatment in pediatric uveitis (Chapter 2), starting with a goniotomy as a first surgical intervention, and if necessary, followed by a second goniotomy procedure. When a failure develops, a GDI (most experience in this patient group is with the Baerveldt GDI and the Ahmed GDI) may be considered. We would not recommend a trabeculectomy or cyclodiode laser for secondary glaucoma in pediatric uveitis.

Importantly, previous studies prior to the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) may have suboptimal control of the uveitis, causing a larger degree of scarring of the trabecular meshwork. Thereby, the outcomes of different types of surgical interventions are difficult to compare over time.

Apart from the type of surgical procedure to be used, it is important to discuss when to use a surgical procedure. In Chapter 3, we describe a high risk of ongoing IOP elevation within one year, when more than two different types of IOP-lowering medications are required. Given this relationship with the use of the amount of IOP-lowering medication, a surgical intervention should be considered when this tipping point is reached, and thus before damage to the optic nerve occurs.

Treatment of uveitis - influence on secondary glaucoma
In the thesis, we report different success rates of surgical interventions, against the background of historical developments. As mentioned before, over the last decade, important developments have occurred in the treatment of pediatric uveitis, and bDMARDs were introduced, resulting in a tremendous improvement of disease control. In addition, knowledge about the essence of inactive uveitis for >3 months has been acquired and applied worldwide (Foster and Rashid 2003; Kok and Barton 2002). These factors may explain the better results after goniotomy in our cohort (described in Chapter 5), compared to older cohorts (described in Chapter 3). Another positive side effect of the use of bDMARDs is the lower prevalence of complications that develop during follow-up (Chapter 6).
In multiple chapters, a steroid induced IOP was seen and measured. The advice to minimize the amount and the duration of the use of topical steroids in these children is still standing, in combination with the low-threshold use of bDMARDs.

**Quality of life**

Pediatric uveitis has a negative impact on the quality of life, because of increased psychological distress, negative coping strategies, and a substantial impact on social and professional perspectives. More objective aspects correlated with a decrease of quality of life are pain after surgery, lower visual acuity, binocular disease, and having had three or more surgical interventions (Chapter 5).

Unfortunately, a QoL questionnaire, specifically validated for patients with pediatric uveitis, is not yet available in Dutch. Another method to gain more knowledge on the impact of the different surgical interventions on the QoL is to include factors that influence the QoL.

For this reason, we evaluated complication rates, number of re-interventions and number of procedures with general anesthesia as outcome variables. Based on the fact that the smaller the number of interventions required, the less negative impact on quality of life, we prefer goniotomy and GDI procedures over cyclodiode laser and trabeculectomy.

**FUTURE PERSPECTIVES**

**Surgical technique**

There are many new developments in the field of surgical procedures, mostly focused on glaucoma in adults. It is important to keep abreast of new developments, but also to keep in mind that children and uveitis patients may respond substantially differently to surgical procedures than patients with open-angle glaucoma. Our preference would be to apply new techniques only in study settings. If large enough numbers are not feasible for enough power to reach a conclusion, centralization and/or collaboration should take place, so that science and knowledge are bundled.

In the field of angle surgery, a special kahook dual blade instrument is developed that can replace the use of a standard needle. The new aspect, compared with the classic goniotomy technique, is the larger treated area and the removal of trabecular meshwork, instead of only cutting the tissue (Elhusseiny et al. 2019; Go and Freedman 2022). However, the potential advantages of removing a part of the trabecular meshwork are doubtable, since part of the meshwork may be needed for a pump
function, to provide an effective aqueous humor outflow (Laroche et al. 2021). A direct comparison of both techniques in pediatric uveitis patients is lacking.

Another variant of angle surgery is gonioscopy-assisted transluminal trabeculotomy (GATT) as performed with guidance of an illuminating microcatheter device (iTrack) (Sachdev et al. 2020). However, whereas goniotomy with the treatment of 180 degrees has encouraging results, the added value of this development in pediatric uveitis patients is doubtful.

In adults, a CO2-laser-assisted sclerectomy as a variant of the deep sclerectomy is described (Xiao et al. 2022). The non-penetrating deep sclerectomy is a variant of the TE, with some experiences in congenital glaucoma, with deroofing of the Schlemm’s canal and exploring the deeper layers, but leaving a very thin layer of sclera over the uveal tissue, in order to prevent a severe hypotony, seen sometimes after a TE (Al-Obeidan et al. 2014; Elhofi and Helaly 2020). Because of the technical challenge of performing this type of procedure, a CO2 laser assist could provide optimal control to create the required scleral flaps. However, because this thesis assumes a superiority of the goniotomy technique over the TE technique, the benefit of deep sclerectomy is also questionable in patients with pediatric uveitis.

In the field of the GDIs, a smaller variant of the Ahmed drainage implant (Ahmed FP7 of 184 mm² versus Ahmed FP8 of 102 mm²) and the Baerveldt drainage implant (350 mm² versus 250 mm²), were already developed and are frequently used in children. In order to minimize postoperative complications such as severe IOP fluctuations, risk of hyphema and in the long term risk of endothelial damage, devices with smaller tubes are designed, based on the mechanism of the well-known GDIs. The Paul implant has a comparably sized 350 mm² plate as the Baerveldt, whereas its tube lumen is smaller (0.1 versus 0.3 mm (Tan et al. 2022). No studies have been published on the use of the Paul implant in children. In children, it would be preferable to also use a smaller plate size in case of a Paul implant, if available. In addition, in adults, in 57% of the patients, the intraluminally placed suture (prolene 6-0) had to be removed, due to a need for more IOP decrease (Vallabh et al. 2022). This extra procedure means a significant disadvantage in children, since this would imply the need for an additional intervention with general anesthesia.

Two devices with very small tube lumen, without a plate, are developed. Smith et al. published a safely implanted XEN gel stent of Allergan Inc in three children with congenital glaucoma, effectively lowering the IOP (Smith et al. 2020). The tube has an external diameter of 150 µm, with an inner diameter of 45 µm. Another small device
(Preserflo Microshunt, Santen USA) was investigated with adequate short-term results (Brandt 2022). Unfortunately, the long-term results are not yet known, but they are important because most tube-related problems do not develop until later. (Chapter 4). In addition, occlusion of the XEN gel tube is described in uveitis patients due to fibrin, which makes a smaller tube potentially more at risk for failure (Gillmann et al. 2018). About these new developments, no comparative data between different GDIs are available.

**Treatment of uveitis - influence on secondary glaucoma**

No comparative studies are yet available to evaluate the impact of different types of DMARDs on the risk of secondary glaucoma and the influence of DMARDs on the outcomes of glaucoma surgery. However, recent studies show positive influences of DMARDs use on the incidence of glaucoma and the outcomes of glaucoma surgery (Wennink et al. 2022; Leinonen et al. 2015).

As stated earlier, the development of uveitic glaucoma is multifactorial, whereas in a short period of time, a reversible steroid-induced IOP increase can develop. In the long run, the scarring of the trabecular meshwork causes the risk of irreversible IOP increase. Scarring, with the formation of fibrosis, is related to multiple inflammatory factors (Durant and Whited 2021). It is to be expected that systemic DMARDs slow down or stop the scarring reaction. However, a more local anti-inflammatory drug that could be used over a longer period of time (without steroids) is essential.

Systemic NSAIDs are a well-known type of drug used in scleritis. Limited research has been done on the use of systemic NSAIDs in patients with uveitis. One study shows that the use of a maintenance dose of systemic NSAIDs decreases the recurrence rate of anterior uveitis in adults (Levinson and Rosenbaum 2010). Several types of eye drops containing nonsteroidal anti-inflammatory drugs (NSAIDs) are available, but previous research mainly focuses on the effects in the treatment of macular edema (Deshka Doycheva, Deuter, and Grajewski 2018; Balasubramaniam et al. 2022). A new eye drop Licaminlimab has recently been developed. This drop is a TNF-alpha inhibitor (bDMARDs), which could potentially suppress anterior uveitis, and thereby also prevent prolonged scarring in the anterior chamber of the eye, without a steroid-induced IOP rise (Pasquali et al. 2022). More research on the use of different types of topical NSAIDs is needed, as they may play a potential prophylactic role in the development of trabecular meshwork scarring over time.

The IOP increase is a response to scarring of the trabecular meshwork. In order to gain more information about the status of scarring in an earlier stage, before influencing
the IOP, a different parameter is necessary. Aqueous humor drainage can be visualized by the fluorescein via the fluorophotometry technique (Toris et al. 1999). The official measurement method involves applying several drops of fluorescein to the cornea to create a corneal deposit. Over a period of several hours, fluorescein diffuses from the cornea into the anterior chamber of the eye, mixes with chamber fluid and begins to drain through the anterior chamber of the eye. Using a fluorophotometer, fluorescein concentrations in the cornea and anterior chamber of the eye are measured periodically over several hours. The log of fluorescein concentrations is plotted over time. The total fluorescein mass in the anterior segment is the product of the fluorescein concentrations in the cornea and anterior chamber and their respective volumes. Then, the aqueous flow rate is calculated by dividing the mass of fluorescein lost from the cornea and anterior chamber over time by the average concentration in the anterior chamber during the time interval (Toris et al. 1999). This principle could be used in children, however, a practically feasible implementation for children has yet to be developed for this purpose. When we measure the aqueous flow repeatedly in patients with the risk of developing secondary glaucoma, the decrease of flow could be detected before the IOP rises, and a goniotomy procedure could be done in an earlier stage. This approach would prevent acute IOP elevation. In addition, treatment can be performed in an elective setting rather than an emergency setting, resulting in fewer consultations, fewer IOP-lowering medications, fewer uncertainties and less risk of optic nerve damage.

Quality of life
To analyze the impact of different surgical interventions on QoL, a questionnaire should be filled out before and at several time points after surgery, depending on the type of surgery. However, to investigate the vision-related quality of life in children with uveitis, an adequate measurement tool is needed.

Different QoL-questionnaires are available, however, a suitable questionnaire for pediatric uveitis with glaucoma is a challenge. First, a visual-based QoL questionnaire is needed. More general health-related QoL questionnaires, like PedQL, are too broad in the themes they address and not specifically aimed at eye-related problems (Wieringa et al. 2021; Haasnoot et al. 2017). Second, a self-reporting questionnaire is preferred, when age permits. Although the experience of the parents is important, literature shows that parents tend to give lower QoL scores than their children about the perception of the child (Wieringa et al. 2021). In our opinion, information about the QoL given by the child itself and additionally by the parents gives the most reliable assessment of the situation. Third, a short questionnaire, which is easy and quick to fill out, is preferable. Fourth, daily-based questions addressing aspects that
examine the ability to participate in traffic/school/sports or the experienced burden of the treatment are relevant. The Effects of Youngsters’ Eyesight on Quality of Life Questionnaire (EYE-Q) could potentially be an adequate measurement instrument (Angeles-Han et al. 2011). However, translation and validation have yet to be finished before it can be used in the Netherlands.

**Quality of evidence**

Due to the very specific target group, unfortunately, our study groups were relatively small and conclusions are based on retrospective analyses. This implies that the risks of bias, inconsistency, and imprecision are considerable. To improve the quality of the evidence, more uniform study designs are needed with a comparable definition of success, time points of measurement, risk factor analysis and complications and re-intervention reports. Studies with a prospective design, larger study groups (in a multicenter design), comparison studies and/or randomized controlled trials would give more reliable evidence about different techniques that can be used in secondary glaucoma in children with chronic uveitis.