Thieme

The Effect of Glaucoma Treatment on Aniridia-Associated Keratopathy (AAK) – A Report from the Homburg Register for Congenital Aniridia

Die Auswirkung der Glaukombehandlung auf die Aniridie-assoziierte Keratopathie (AAK) – Ein Bericht aus dem Homburger Register für kongenitale Aniridie

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ABSTRACT

Background Congenital aniridia is a severe malformation of almost all eye segments. Aniridia-associated keratopathy (AAK) and secondary glaucoma, which occur in more than 50% of affected individuals, are typically progressive and pose a high risk of blindness for patients with congenital aniridia. Our aim was to investigate the effect of glaucoma treatment on AAK in patients of the Homburg Aniridia Center.

Methods Our retrospective monocentric study included patients who underwent a comprehensive ophthalmological examination at the Homburg Aniridia Center between June 2003 and January 2022.

Results There were 556 eyes of 286 subjects (20.1 ± 20.1 years; 45.5% males) included. In 307 (55.2%) eyes of 163 subjects (27.5 ± 16.3 years; 43.1% males), glaucoma was present at the time of examination. The mean intraocular pressure in the glaucoma group was 19.0 mmHg (± 8.0), while in the non-glaucoma group, it was 14.1 mmHg (± 3.6) ($p < 0.001$). In the glaucoma group, 68 patients used antiglaucomatous topical monotherapy, 51 patients used 2 agents, 41 patients used 3 agents, 7 patients used quadruple therapy, and 140 did not use topical therapy (e.g., after pressure-lowering surgery, pain-free end-stage glaucoma, or incompliance). Patients were classified according to the following stages of AAK: Stage 0 (96 eyes [17.2%], no keratopathy), Stage 1 (178 eyes [32.0%]), Stage 2 (107 eyes [19.2%]), Stage 3 (67 eyes [12.0%]), Stage 4 (62 eyes [11.1%]), Stage 5 (45 eyes [8.0%]). The mean stage of AAK was 1.4 (1.2–1.5) in the group without eye drops, 1.9 (1.5–2.2) in the group with

monotherapy, 1.8 (1.5–2.1) in the group with 2 drugs, 1.9 (1.5–2.2) in the group with 3 drugs, 3.4 (2.3–4.6) in the group with 4 drugs, and 3.3 (3.1–3.6) after antiglaucomatous surgery. The stage of AAK was significantly positively correlated with the number of pressure-lowering eye drops ($p < 0.05$) and prior pressure-lowering surgery ($p < 0.05$). Prostaglandin analogues were not correlated with a higher AAK stage compared to the other drug groups.

Conclusions At the Homburg Aniridia Center, patients using topical antiglaucomatous quadruple therapy or who had previously undergone antiglaucomatous surgery had by far the highest AAK stage. The different drug groups had no influence on the AAK stage.

ZUSAMMENFASSUNG

Hintergrund Die kongenitale Aniridie ist eine schwere Fehlbildung fast aller Augensegmente. Insbesondere die Aniridie-assoziierte Keratopathie (AAK) sowie das bei mehr als 50 % der Betroffenen auftretende Sekundärglaukom verlaufen typischerweise progressiv und stellen ein hohes Risiko der Erblindung für Patienten mit kongenitaler Aniridie dar. Unser Ziel war es, bei Patienten des Homburger Aniridie-Zentrums die Auswirkung der Glaukombehandlung auf die AAK zu untersuchen.

Methoden Unsere retrospektive, monozentrische Studie umfasste Patienten, die sich zwischen Juni 2003 und Januar 2022 einer umfassenden augenärztlichen Untersuchung durch das Homburger Aniridie-Zentrum unterzogen.

Ergebnisse Es wurden 556 Augen von 286 Probanden (20,1 ± 20,1 Jahre; 45,5 % Männer) eingeschlossen. Bei 307 (55,2 %) Augen von 163 Patienten (27,5 ± 16,3 Jahre; 43,1 % Männer) lag zum Zeitpunkt der Untersuchung ein Glaukom vor. Der Augeninnendruck lag in der Glaukomgruppe im Mittel bei 19,0 mmHg (± 8,0) während er bei den Patienten ohne Glaukom bei 14,1 mmHg (± 3,6) lag ($p < 0,001$). In der Glaukomgruppe nutzten 68 Patienten eine lokale antiglaukomatöse Monotherapie, 51 Patienten nutzten 2 Wirkstoffe, 41 Patienten nutzten 3 Wirkstoffe, 7 Patienten nutzten eine Vierfachtherapie, 140 nutzten keine Lokaltherapie (z. B. nach drucksenkender Operation, schmerzfreies Glaukom-Endstadium oder Incompliance). Die Patienten wurden nach den folgenden Stadien der Aniridie-assoziierten Keratopathie (AAK) eingeteilt: Stadium 0 (96 Augen [17,2 %], keine Keratopathie), Stadium 1 (178 Augen [32,0 %]), Stadium 2 (107 Augen [19,2 %]), Stadium 3 (67 Augen [12,0 %]), Stadium 4 (62 Augen [11,1 %]), Stadium 5 (45 Augen [8,0 %]). Das Stadium der Aniridie-assoziierten Keratopathie lag in der Gruppe ohne Augentropfen im Mittel bei 1,4 (1,2–1,5), in der Gruppe mit Monotherapie bei 1,9 (1,5–2,2), in der Gruppe mit 2 Wirkstoffen bei 1,8 (1,5–2,1), in der Gruppe mit 3 Wirkstoffen bei 1,9 (1,5–2,2), in der Gruppe mit 4 Wirkstoffen bei 3,4 (2,3–4,6) und nach antiglaukomatöser Operation bei 3,3 (3,1–3,6). Das Stadium der Aniridie-assoziierten Keratopathie war signifikant positiv korreliert mit der Anzahl der drucksenkenden Augentropfen ($p < 0,05$) und einer zuvor durchgeführten drucksenkenden Operation ($p < 0,05$). Prostaglandinanaloga waren im Vergleich zu den anderen Wirkstoffgruppen nicht mit einem höherem AAK-Stadium korreliert.

Schlussfolgerungen Im Homburger Aniridie-Zentrum wiesen die Patienten, die eine lokale antiglaukomatöse Vierfachtherapie nutzten oder zuvor antiglaukomatös operiert wurden mit Abstand das höchste AAK-Stadium auf. Die verschiedenen Wirkstoffgruppen hatten keinen Einfluss auf das AAK-Stadium.

Introduction

The introduction as well as the patients and methods section of this study have already been described and published in detail [1]. The authors therefore limit themselves to presenting an abbreviated topic-specific manuscript.

Congenital aniridia is a hereditary bilateral ocular disorder characterized by autosomal dominant inheritance. During a lifetime, over 50 % of patients with aniridia will develop aniridia-associated glaucoma. While open-angle glaucoma is more prevalent in individuals with aniridia, there have also been reports of anatomical malformations linked to the underdeveloped iris obstructing the trabecular meshwork [2 – 4].

Diagnosing and monitoring aniridia-associated glaucoma present challenges due to the presence of keratopathy, nystagmus, and foveal and optic nerve head hypoplasia. Topical glaucoma therapy for aniridia does not significantly differ from general glaucoma treatment; however, the use of preservative-free formulations is recommended. Often, monotherapy alone proves insufficient, necessitating a combination of treatments. In case the effect of conservative treatment is not sufficient, an antiglaucomatous surgical intervention may become necessary [5 – 8].

Nevertheless, in case of a painless eye, without light perception, there is no more necessity of antiglaucomatous surgery. Since congenital aniridia is characterized by a pathologically altered conjunctiva, a more or less evident inflammatory state and healing disorders due to limbal stem cell insufficiency, the risks of glaucoma surgery are significantly higher, and the interval of surgically induced pressure reduction is usually shorter compared to non-aniridia (glaucoma) patients [6, 8, 9]. In our clinical routine, trabeculotomy is considered the primary option if the anatomy of the chamber angle permits [6, 8]. Otherwise, trabeculectomy is an option, but drainage implants are also effective in lowering intraocular pressure (IOP) [10]. In severely damaged eyes, cyclophotocoagulation can be performed as the last option, whereby aniridia fibrosis syndrome and phthisis bulbi are feared complications [4, 8].

There is limited literature on glaucoma therapy specifically for congenital aniridia and no randomized controlled studies have explored the efficacy of different treatment options and their evidence-based use in this context. The progression of keratopathy further complicates glaucoma follow-up assessments, as it leads to diminishing visual clarity and must, therefore, be taken into consideration when devising a glaucoma treatment plan [8, 9].

The purpose of this cross-sectional study was to compare the different substance classes with regard to their effect on the AAK in order to create more evidence for therapy recommendations.

Patients and Methods

Ethical considerations

Our retrospective single-center study included patients at the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar, Germany. This study was approved by the Ethics Committee of Saarland/Germany (No 144/15) and followed regulations of the Declaration of Helsinki. Informed consent was obtained from all participants. In case of minors or guardianship, informed consent was obtained from the legal representative or legal guardian.

Diagnosis of glaucoma

As there are some disease specifics to consider when examining aniridia patients, we would like to go into more detail about the convention we use regarding the presence of glaucoma. The classical definition of glaucoma includes the triad of increased IOP, nerve fiber damage, and visual field loss. We also used these criteria in order to define glaucoma disease within our congenital aniridia patients. Nevertheless, we were confronted with several difficulties during examination of congenital aniridia subjects.

Due to nystagmus and large daily fluctuations in ocular surface integrity, the visual field examination is very stressful for aniridia patients without providing satisfactory reproducibility to determine progression. Our examination and clinical evaluation therefore focus mainly on the morphology and morphological changes of the optic nerve head during progression, taking into account IOP. Both increasing optic disc excavation in the presence of increased IOP (over 21 mmHg) and increasing optic disc excavation in the presence of non-increased IOP (neurological cause excluded) are considered by us to be positive for the presence of glaucoma. Taking optic disc photos regularly facilitates the assessment of excavation progression. The measurement of the nerve fiber layer thickness by means of optical coherence tomography is included as a supportive measure. Here, too, it must be borne in mind in congenital aniridia that due to congenital optic nerve anomalies (often hypoplastic), a single measurement does not allow any conclusion to be drawn about increasing damage to the nerve cells, but only the evaluation of several examinations in the course allows this assessment to be made. In this context, morphological assessment and diagnosis should be reserved for an experienced examiner. Frequent changes of the examiner should also be avoided in order not to complicate the assessment of the course. This was taken into account and implemented in our department.

Inclusion criteria, data collection, and examination methods

Inclusion criterion was the presence of partial or complete congenital aniridia, visible at slit lamp examination. All subjects underwent a structured ophthalmic examination through the head of the KiOLoN ("Kinderophthalmologie", Orthoptics, Low Vision and Neuroophthalmology) Unit of the Department of Ophthalmology of Saarland University (Prof. Dr. Barbara Käsmann-Kellner). Uncorrected and best-corrected visual acuity (UCVA and BCVA) measurements using Snellen charts, IOP measurement using Goldmann applanation tonometry or iCare (Icare Finland Oy, Vantaa, Finland), and detailed slit lamp and fundus examinations were performed. If there was sufficient cooperation, a measurement was taken using Goldmann applanation tonometry, whereas younger children were more likely to be measured using iCare. For the refinement of the IOP measurement, the Dresden correction table according to Kohlhaas was used to compensate for systematic measurement errors caused by a change in corneal thickness [11].

AAK was classified as follows: Stage 0 (no limbal changes), Stage 1 (conjunctival tissue just crosses the limbal border but remains 1 mm or less from the limbus), Stage 2 (the pannus extends across the peripheral cornea and is typically present in 360 degrees of the cornea), Stage 3 (the pannus invades the central cornea, typically covering the entire cornea with vessels), Stage 4 (the cornea is completely vascularized), Stage 5 (end-stage with an opaque, thick, vascularized cornea) [1, 12]. In the evaluation of the eye drops, mono preparations were evaluated as one eye drop, and combination preparations were assigned according to their active ingredients and were accordingly included in the evaluation as two eye drops. This made it possible to evaluate the different substance classes in relation to each other.

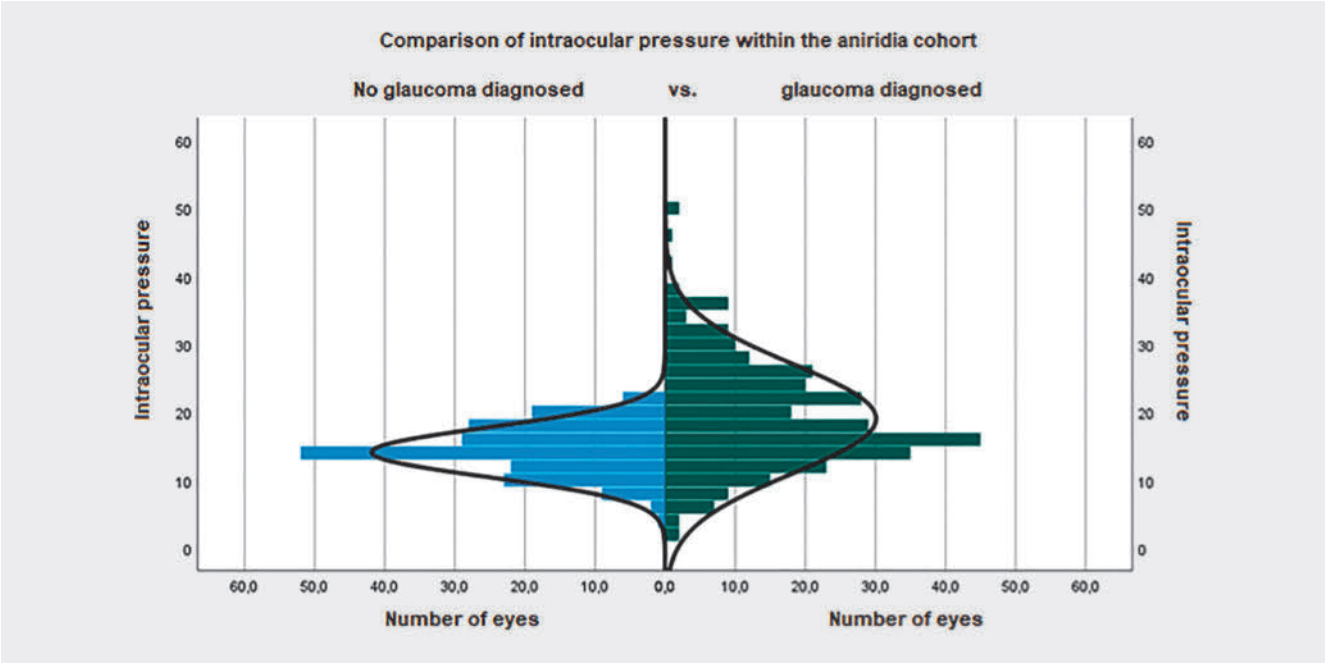
All patient data were entered pseudonymized in a Microsoft Access database. Data analysis was performed using IBM SPSS Statistics for Windows Version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to characterize data and assess the distribution of study variables. Categorical variables were summarized in frequencies or percentages. A chi-square test was performed to check for the presence of an association between dependent variables and independent variables, a t-test was used to compare normally distributed variables, and a Pearson correlation was used after adjusting for confounding variables to describe the correlation between the identified risk factors and the progression of AAK. The statistical significance was considered at a p value < 0.05 and a 95% confidence interval (CI).

In collaboration with the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar (Chair: Prof. Dr. B. Seitz) and the Dr. Rolf M. Schwiete Center for Limbal Stem Cell and Aniridia Research, Homburg/Saar (Chair: Prof. Dr. N. Szentmáry), our aim was to build up a database in order to get a better insight into the pathomechanisms and stage-appropriate treatment options of congenital aniridia.

The present study summarizes patient data for subjects examined between June 2003 and January 2022.

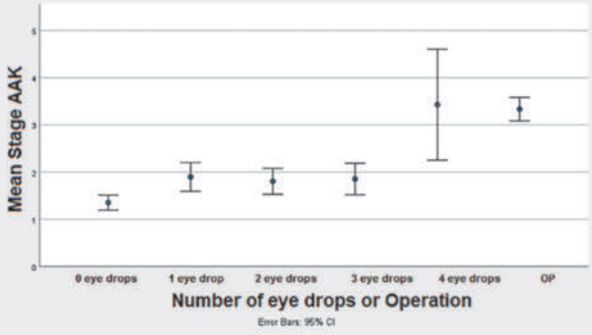
Results

There were 556 eyes of 286 subjects (20.1 ± 20.1 years; 45.5% males) included. In 307 (55.2%) eyes of 163 subjects (27.5 ± 16.3 years; 43.1% males), glaucoma was present at the time of examination. The mean IOP in the glaucoma group was 19.0 mmHg (± 8.0), while in the non-glaucoma group, it was 14.1 mmHg (± 3.6; $p < 0.001$, ▶ **Fig. 1**). In the glaucoma group, 68 (20.5%)



▶ **Fig. 1** Combined histogram showing intraocular pressure distribution of subjects at the Homburg Aniridia Center. The patients with glaucoma are shown in green (right), the others are shown in blue (left).

patients used topical monotherapy, 51 (16.6%) patients used 2 agents, 41 (13.4%) patients used 3 agents, 7 (2.3%) patients used quadruple therapy, and 140 (45.6%) did not use topical therapy (e.g., after pressure-lowering surgery or pain-free end-stage of glaucoma). Patients were classified according to the following stages of AAK: Stage 0 (96 eyes [17.2%], no keratopathy), Stage 1 (178 eyes [32.0%]), Stage 2 (107 eyes [19.2%]), Stage 3 (67 eyes [12.0%]), Stage 4 (62 eyes [11.1%]), Stage 5 (45 eyes [8.0%]) [1]. The mean stage of AAK was 1.4 (1.2–1.5) in the group without eye drops, 1.9 (1.5–2.2) in the group with monotherapy, 1.8 (1.5–2.1) in the group with 2 drugs, 1.9 (1.5–2.2) in the group with 3 drugs, 3.4 (2.3–4.6) in the group with 4 drugs, and 3.3 (3.1–3.6) after antiglaucomatous surgery. The stage of AAK was significantly positively correlated with the number of pressure-lowering eye drops ($p < 0.05$) and prior antiglaucomatous surgery ($p < 0.05$; (▶ **Fig. 2**). Even after correction for age, there was still a significant correlation between the number of eye drops and AAK stage ($r = 0.166$ and $p < 0.001$, Pearson correlation). After previous corneal surgery (PKP, PTK, AMT, pannus abrasion), no correlation between glaucoma therapy and AAK stage was found (▶ **Fig. 3**). Prostaglandin analogues were not correlated with a higher AAK stage compared to the other drug groups, despite their proinflammatory side effect ($p > 0.05$).

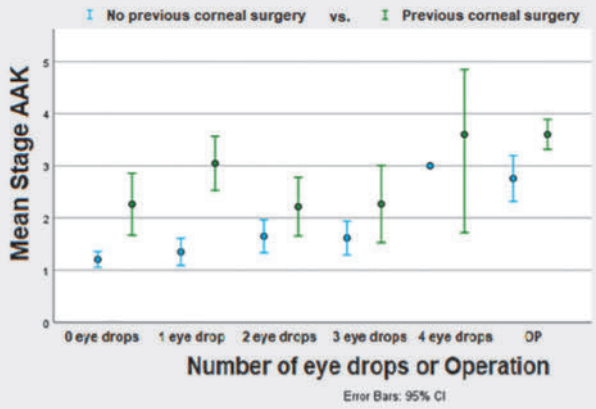


▶ **Fig. 2** Comparison of stage of aniridia-associated keratopathy (AAK) considering the glaucoma therapy.

Discussion

Keratopathy and glaucoma are considered the main causes of secondary blindness in the context of congenital aniridia. Both pathologies are progressive and require different therapeutic approaches [5–9, 13]. So far, there are only a few studies dealing with secondary glaucoma in the context of congenital aniridia [14, 15]. The incidence of glaucoma in aniridia is reported to be 50–75% [3, 16]. Our experience confirms these descriptions also in the present larger cohort, with an incidence of 55.2% regarding the presence of glaucoma overall.

Limbal stem cell insufficiency and altered ocular surface as well as a continuous inflammatory processes are discussed as the cause of the progression of keratopathy [17–25]. Therefore, there is a consensus among experts to use preservative-free preparations for topical therapy, if possible, in order to avoid aggravation of the inflammatory state by proinflammatory additives such as benzalkonium chloride [6–8, 12].



▶ **Fig. 3** Comparison of stage of aniridia-associated keratopathy (AAK) considering the glaucoma therapy correcting for previous corneal surgery (PKP, PTK, AMT, pannus abrasion). The patients who did not have any previous corneal surgery are represented in blue, the patients who did have previous corneal surgery before assessment are represented in green.

Despite these precautions, more intensive pressure-lowering topical therapy seems to be associated with a higher stage of AAK. However, no comparative studies are currently available that would allow a closer discussion against the background of already published literature.

Prostaglandin analogues have established themselves as the most effective substance class in general glaucoma therapy but are well known for their undesirable proinflammatory effects. Interestingly, no difference between the individual substance classes (beta-blockers, alpha-agonists, carbonic anhydrase inhibitors, prostaglandin analogues) and AAK could be demonstrated in the present study. It should be taken into account that due to the division of our cohort into smaller subgroups, small differences may no longer be evident for statistical reasons. For this reason, the available data do not allow us to make a reliable statement about a causative impact of a pressure-lowering substance class on the stage of AAK.

However, a closer look at our larger group of patients suggests that there is a correlation between advanced glaucoma or the need for more intensive pressure-lowering therapy and the progression of keratopathy. A significant difference was found for the number of pressure-lowering eye drops, whereby patients who were not (or no longer) dependent on topical therapy or who did not apply eye drops due to noncompliance showed the least pronounced AAK. No significant difference was found between monotherapy, double therapy, and triple therapy. However, it should be pointed out that larger numbers of cases and further studies are necessary to be able to make a reliable statement. The most advanced keratopathy was seen in patients with quadruple therapy and after antiglaucomatous surgery. This clinical observation alone does not yet allow us to draw any conclusions about the pathomechanism and can therefore only be seen as a suggestion for future basic research studies. In addition, a specific approach is necessary in order to verify glaucoma progression in time. Due to the very small number of patients, a further differentiation between the surgical procedures (e.g., trabeculotomy, trabeculectomy, cyclophotocoagulation, drainage implant) is currently not considered useful and is therefore not discussed further.

Our goal is to include more patients in our registry and to validate the previously observed trends with larger numbers of cases and in the long-term follow-up in terms of a longitudinal study outline.

CONCLUSION BOX

Already known:

- In congenital aniridia, there is an increased risk of developing blindness during life.
- AAK and glaucoma are the most common causes of blindness in congenital aniridia.
- In order to develop better treatment options in congenital aniridia, establishment of an aniridia register is necessary.

Newly described:

- A more intensive pressure-lowering topical therapy is associated with a higher stage of AAK.
- AAK stage of patients that had previously undergone glaucoma surgery was comparable to patients who used antiglaucomatous topical quadruple therapy.
- Our aniridia register will support further validation of previously observed trends with growing numbers of cases.

Conclusions:

At the Homburg Aniridia Center, patients using topical antiglaucomatous quadruple therapy or who had previously undergone pressure-lowering surgery had the highest AAK stage. The different drug substance groups had no influence on the AAK stage. Our registry will allow further detailed analysis of ophthalmic and systemic disease in patients with congenital aniridia over the long term.

Conflict of Interest

The authors declare that they have no conflict of interest.

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