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OPHTHALMIC AND SYSTEMIC SIGNS OF CONGENITAL ANIRIDIA

PhD thesis

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List of abbreviations

AMT	amniotic membrane transplatation
ANOVA	analysis of variance
AFS	aniridia fibrosis syndrome
AAK	aniridia associated keratopathy
BCVA	best corrected visual acuity
BMI	body mass index
CA	congetinal aniridia
CTR	capsular tension ring
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	fundus autofluorescence
GLM	generalized linear model
HLA	human leukocyte antigen
KiOLoN	Kinderophthalmologie, Orthoptics, Low Vision and Neuroophthalmology
ILD	iris-lens diaphragm
IOL	intraocular lens
IOP	intraocular pressure
LSC	limbal stem cells
LSCD	limbal stem cell deficiency
MGD	Meibomian gland dysfunction
OCT	optical coherence tomography
OSDI	Ocular Surface Disease Index
PAX6	paired box 6
PCL	posterior chamber lens
PKP	penetrating keratoplasty
UCVA	uncorrected visual acuity
WAGR syndrome	Wilms tumor, aniridia, genitouretery anomalies, retardation
VA	visual acuity
VEP	visual evoked potential

1. Introduction

1.1. Congenital Aniridia – A Spectrum Disorder

Although the most recognizable feature of congenital aniridia is iris hypoplasia, the condition represents a far more complex disorder than its name suggests. Congenital aniridia affects nearly all ocular structures and is associated with a wide spectrum of ophthalmic as well as systemic abnormalities (1). In approximately 90% of cases, the disease results from autosomal dominant pathogenic variants in the *PAX6* gene (11p13), although sporadic occurrences are also observed. It is classified as a rare genetic disorder, with an estimated prevalence ranging from 1 in 40,000 to 1 in 100,000 individuals (2).

Different ocular phenotypes were observed, each exhibiting distinct pathologies and varying degrees of severity. The correlation between genotype and phenotype remains insufficiently understood and warrants further investigation. Owing to its high variability and expressivity, congenital aniridia can be best characterized as a spectrum disorder (1,3).

1.1.1. Ophthalmic manifestations of congenital aniridia

The ophthalmic manifestations of congenital aniridia-beyond the characteristic iris malformations that range from partial coloboma to complete iris absence-include aniridia-associated keratopathy (AAK), congenital or juvenile cataract, secondary glaucoma, and hypoplasia of the macula or optic nerve head (4). Visual acuity varies considerably among individuals with aniridia: while some patients present with congenital abnormalities that limit vision from birth, others experience progressive visual decline due to secondary ocular complications that develop over time (5).

Iris malformations

The most readily recognizable feature of congenital aniridia (CA) is iris hypoplasia, which can be identified during slit-lamp examination. The degree of iris malformation is highly variable, ranging from an irregular pupillary margin (grade 0) to atypical coloboma (grade 1), partial aniridia with visible iris remnants under slit-lamp examination (less than 6 clock hours in grade 2, more

than 6 clock hours in grade 3), and complete aniridia (grade 4) (6). In most cases, however, residual iris stumps can still be visualized by gonioscopy (2).

Although visual acuity (VA) is not directly affected by the degree of iris hypoplasia alone, patients frequently report photophobia, impaired depth perception, and, not insignificantly, cosmetic concerns, depending on the severity of the defect (2). While implantable iris prostheses might appear to offer a straightforward therapeutic solution to these issues, studies have shown that such devices are mostly associated with serious postoperative complications, including the progression of AAK and glaucoma (7). Tinted or colored contact lenses may alleviate photophobia; however, their use is frequently contraindicated in patients with advanced stages of keratopathy (2).

Aniridia associated keratopathy

AAK represents a distinct form of corneal disease characteristic of CA (8). The prevalence of AAK, at varying stages of severity, has been reported to reach approximately 80% among affected individuals (9). The condition is progressive, leading to gradual and often significant visual decline over time. Its pathogenesis is multifactorial, involving limbal stem cell deficiency (LSCD), impaired corneal wound healing, and loss of corneal sensitivity, all of which contribute to the development and progression of this complex corneal pathology (8).

Glaucoma

Glaucoma occurs in approximately 20-70% of patients with CA. It may arise from congenital malformations of the trabecular meshwork and Schlemm's canal, the formation of anterior synechiae, or anterior rotation of the residual iris stump, all of which contribute to impaired aqueous outflow and elevated intraocular pressure (10).

Cataract

In patients with CA, lens opacities may be present at birth or develop during the first two decades of life, with a reported prevalence of 50-90% (2,11). These cataracts are most commonly of the anterior or posterior polar type. Typically, there is a congenital anterior polar cataract. Then, a posterior polar opacity appears, followed by the development of subcapsular flecks and radial

streaks, which progressively extend toward the posterior pole to form the characteristic “cartwheel” pattern (4,12).

Although cataract surgery often results in temporary improvement of visual acuity (VA), reports indicate a concerning incidence of postoperative complications in patients with CA, raising questions about the overall benefit of such procedures in this population (12,13).

Nystagmus and fovea hypoplasia

Nystagmus in CA is a secondary manifestation resulting from foveal hypoplasia, where the sensory deficit leads to poor fixation and unstable gaze. Foveal hypoplasia can be detected in most *PAX6*-positive patients (81-91%) using foveal optical coherence tomography (OCT) or fundus autofluorescence (FAF) imaging, which typically reveals the absence of the foveal avascular zone (14). In affected children, the degree of foveal hypoplasia largely determines future VA (2,15).

1.1.2. Systemic manifestations of congenital aniridia

Systemic manifestations in CA may occur independently or as part of a broader syndromic presentation. Among these, the most common association is the WAGR syndrome, characterized by Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability (2,4,16). Another, less frequent entity is Gillespie syndrome, which presents with bilateral aniridia and cerebellar ataxia (2,4,16).

Auditory deficits have also been reported in children with *PAX6* pathogenic variants and aniridia. These impairments can reduce the ability to localize and comprehend speech in noisy environments, further increasing vulnerability in individuals who already suffer from reduced VA (2,4,16).

Experimental studies in murine models have revealed that *PAX6* pathogenic variants can lead to endocrine dysfunction due to decreased pancreatic hormone secretion, suggesting broader systemic involvement. In human studies, obesity and elevated body mass index (BMI) have shown a positive correlation with aniridia, indicating that metabolic dysregulation may also form part of the systemic phenotype (2,4,16).

1.2. The significance of aniridia associated keratopathy

AAK is a distinct corneal disorder characteristic of CA, developing in the majority of patients (approximately 80%), and therefore has a profound impact on visual function and quality of life in this population (17).

In the pathophysiology of AAK, dysfunction of the limbal stem cell niche is thought to play a crucial role. Impaired epithelial proliferation leaves the cornea structurally and functionally vulnerable. In addition, tear film instability, arising from reduced corneal sensitivity and Meibomian gland dysfunction, further compromises the already fragile ocular surface (8). Despite significant progress in understanding this condition, it remains unclear whether these alterations result directly from *PAX6* pathogenic variants or represent secondary consequences of the underlying genetic defect. Further research is needed to clarify this relationship (18).

Clinically, the disease typically begins with the formation of fine neovascular vessels in the limbal area. These vessels progressively invade the cornea in a centripetal pattern, extending toward the central cornea. Alongside this superficial vascular ingrowth, the keratopathy gradually extends into deeper stromal layers. Recurrent epithelial erosions and ulcerations often occur, leading to subepithelial haze formation, stromal fibrosis, and ultimately to the development of an irregular, opaque, and thick fibrovascular pannus (18,19).

Accurate grading of AAK severity is essential for monitoring disease progression, selecting the most appropriate therapeutic approach, whether conservative or surgical, and for informing patients about their prognosis and treatment options (20).

1.3. Cataract surgery in congenital aniridia

Previous studies have reported conflicting outcomes regarding the efficacy and safety of cataract surgery in patients with CA. Complications may include the progression of AAK, the onset or worsening of glaucoma, and the development of the severe aniridia fibrosis syndrome (AFS) that is characterized by fibrotic transformation of the lens capsule following intraocular surgery, which in advanced cases may ultimately lead to phthisis bulbi. (12,13). Because the early stages of cataract formation in CA often do not significantly affect VA, and given the complex

pathophysiology and risk of severe postoperative complications, the indications and timing of cataract surgery in these patients require careful evaluation and further research (4).

2. Objectives

2.1. To determine the prevalence and spectrum of ocular manifestations in CA by analyzing patient data from a Hungarian tertiary care center, and to identify systemic pathologies associated with CA through the evaluation of data from both a Hungarian tertiary care center and the Homburg Aniridia Center.

2.2. To evaluate the stages of AAK in Hungarian patients using established literature-based classification systems.

2.3. To assess the impact of cataract surgery on VA, AAK stage, and the presence or progression of glaucoma in patients with CA at the Homburg Aniridia Center.

3. Methods

3.1. Examination of ocular and systemic comorbidities in congenital aniridia: data from Hungary and Germany

Regarding our Hungarian cohort, all procedures adhered to the principles of the Declaration of Helsinki, and the study was approved by the Semmelweis University Regional and Institutional Scientific and Ethics Committee (approval number: 80/2020). Participation in the study was voluntary, and written informed consent was obtained from all participants or, in the case of minors, from their legal guardians (1).

Patients diagnosed with or treated for congenital aniridia at the Department of Ophthalmology, Semmelweis University between October 2005 and May 2022 were identified using the Medsolution electronic medical record system (T-Systems Magyarország Zrt., Budapest). The identified patients were subsequently invited to participate in a comprehensive ophthalmic examination (1).

A detailed medical history was collected, focusing on both ocular and systemic comorbidities. In addition, participants completed the Ocular Surface Disease Index (OSDI) questionnaire to evaluate the severity of dry eye symptoms, categorized as normal (0-12 points), mild (13-22 points), moderate (23-32 points), and severe (33-100 points) (1).

A comprehensive ophthalmic examination followed. VA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and uncorrected visual acuity (UCVA) values were used for analysis. Intraocular pressure (IOP) was measured with the iCare tonometer (CenterVue S.p.A., Padova, Italy). A detailed slit-lamp examination was performed, and the corneal status was documented photographically. Foveal and optic nerve imaging was obtained using OCT (AngioVue OCTA, RTVue XR Avanti, OptoVue, Fremont, CA, USA), and ultrasound biomicroscopy was conducted with 10 MHz and 20 MHz probes (Ultrascan, Alcon, Fort Worth, TX, USA) (1).

Regarding our German cohort, our study at the Homburg Aniridia Centre was approved by the Ethics Committee of Saarland (No. 144/15), and followed the guidelines described in the Declaration of Helsinki. In this study, patients with congenital aniridia who visited the Department of Ophthalmology of Saarland University Medical Center in Homburg/Saar, Germany, from June

2003 were included. The systemic anamnestic data were extracted from the medical records, into a database (16).

3.2 Examination of the stages of aniridia associated keratopathy in congenital aniridia in a Hungarian cohort

All procedures adhered to the principles of the Declaration of Helsinki, and the study was approved by the Semmelweis University Regional and Institutional Scientific and Ethics Committee (approval number: 80/2020). Participation in the study was voluntary, and written informed consent was obtained from all participants or, in the case of minors, from their legal guardians (20).

The corneal status of each patient was documented by slit-lamp examination, and the observed corneal abnormalities were classified according to the staging systems proposed by Mackman (21), López-García (22), Lagali (18,19) and Mayer (23,24).

The earliest classification was introduced by *Mackman* in 1979, who described three stages (0-2) of AAK. In stage 0, no corneal abnormalities are visible under slit-lamp examination. Stage 1A is characterized by one or more non-continuous superficial pannuses originating from the limbus, whereas in stage 1B, pannuses encircle the cornea concentrically at 360 degrees without central involvement. The most advanced form, stage 2, is defined by central pannus formation accompanied by marked stromal scarring (20,21).

In *Mayer's* classification (2003), fluorescein staining is incorporated to improve diagnostic sensitivity. In stage 1, no abnormalities are visible under white light, but delayed fluorescein staining reveals areas of epithelial irregularity. Stage 2 is characterized by epithelial lesions in a circular peripheral pattern, while the corneal center remains clear. In stage 3, epithelial abnormalities extend to the central cornea, accompanied by superficial peripheral vascularization. Stage 4 includes the appearance of subepithelial opacities, and in the final stage 5, a fibrovascular pannus becomes evident across the cornea (20,23,24).

López-García (2006) proposed a simplified three-stage system. In stage 1, the pannus extends ≤ 1 mm beyond the limbus. Stage 2 is defined by pannus involvement of at least half of the corneal periphery, with possible subepithelial opacity. In stage 3, the central cornea becomes affected (20,22).

The most recent and widely adopted system is that of *Lagali et al.*, first published in 2018 and revised in 2020 (18,19). This model divides AAK into four grades. In grade 0, no abnormalities are observed under slit-lamp examination. In grade 1, conjunctival tissue and blood vessels cross the limbus by ≤ 1 mm. In grade 2, the neovascularization and conjunctivalization advance toward the corneal center but spare the central 2-3 mm. In grade 3, the blood vessels reach the corneal center, and grade 4 represents the most advanced stage, characterized by a dense, opaque, and irregular fibrovascular pannus (18,20).

3.3. Examination of the effect of lens surgery in patients with congenital aniridia: data from the Homburg Aniridia Centre

This retrospective, single-center study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Saarland, Germany (approval no. 144/15).

The study included patients with congenital aniridia examined at the Department of Ophthalmology, Saarland University Medical Center, Homburg/Saar, Germany. All participants underwent comprehensive ophthalmic evaluation between June 2003 and January 2022 at the KiOLoN Unit (Kinderophthalmologie, Orthoptics, Low Vision and Neuroophthalmology) of the Department of Ophthalmology (25).

For this retrospective analysis, data on VA, slit-lamp findings, grading of AAK, and glaucoma assessment were extracted from medical records. Baseline (first examination) data were pseudonymized and integrated into the Homburg Aniridia Center database (25).

Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were assessed using either a Snellen chart, the Worth Ivory Ball test, or the Landolt broken ring chart in pediatric cases. For this study, since UCVA or BCVA data were not uniformly available for all patients, “visual acuity (VA)” was defined as the better value of UCVA or BCVA, expressed in logMAR units (25).

A detailed slit-lamp examination of the anterior segment was performed in all cases. When ocular media clarity allowed, fundoscopy was conducted to assess the posterior segment. AAK was classified according to Lagali et al. (18,19).

IOP was measured using Goldmann applanation tonometry, iCare tonometry (Icare Finland Oy, Vantaa, Finland), or other validated methods. Glaucoma was defined according to Fries et al.

patients were classified as glaucomatous if they received anti-glaucoma medication, had undergone glaucoma surgery, or presented with IOP >22 mmHg. Assessment of optic nerve fiber loss or visual field defects was not feasible in most cases due to young age, nystagmus, or media opacity (6,25).

The examined eyes were grouped according to lens status as follows: clear lens, cataract (any type or stage), pseudophakic, aphakic, and subluxated lens. Additionally, patients were categorized into age subgroups (0-10 years, 10-20 years, 20-40 years, and >40 years) to analyze VA, AAK stage, and glaucoma prevalence across different life stages.

All statistical analyses were performed using IBM SPSS Statistics, Version 28 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic and clinical data. The effect of lens status on VA and IOP was assessed using one-way analysis of variance (ANOVA). Post hoc comparisons were conducted with Dunnett's test for VA and with the Bonferroni test for IOP to identify significant differences between groups. Associations between lens status, AAK stage, and presence of glaucoma were analyzed using the chi-square test. To account for potential confounding effects of age, a generalized linear model was applied to evaluate the influence of lens status on VA and IOP while controlling for age as a covariate. In addition, the Kruskal–Wallis test, followed by chi-square post hoc analysis, was used to examine the relationship between age and lens categories, and to compare AAK stages and glaucoma prevalence across different age groups. A p-value of <0.05 was considered statistically significant (25).

4. Results

4.1. Examination of ocular and systemic comorbidities in congenital aniridia: data from Hungary and Germany

Of the 82 patients identified in the Hungarian database, 33 patients presented for outpatient examination. A detailed ophthalmological and systemic history was obtained from all 33 patients, and a total of 65 eyes were examined, one patients' one eye had been previously enucleated. The mean age of participants was 25.69 ± 17.49 years (range: 5-59 years). The study population consisted of 17 females (51.5%) and 16 males (48.5%). A summary of the ocular and systemic findings is provided in **Tables 1 and 2** (1).

The mean OSDI score was 4.03 ± 6.39 . The mean vision-related subscore was 3.09 ± 7.21 , and the mean environmental factor subscore was 4.82 ± 6.54 . Based on the OSDI classification, 30 patients (90.9%) were within the normal range (0-12 points) for dry eye symptoms, 2 patients (6.1%) reported mild symptoms, and 1 patient (3.0%) showed moderate symptoms. Severe dry eye disease was not observed in any participant.

Nystagmus was detected in 45 eyes of 23 patients (69.2%). The UCVA was 0.14 ± 0.13 (0.9 logMAR; range: 0.63-0.005). In 6 eyes of 4 patients (9.2%), UCVA was below 0.1. On slitlamp examination, eyelid inflammation and Meibomian gland dysfunction were each observed in 35 eyes (53.9%). Evaluation of the cornea revealed epithelial staining defects in 4 eyes (6.2%). Salzmann's nodular degeneration was observed in 15 eyes (23.1%). No pseudopterygium was identified in any case. The mean IOP at the time of examination was 21.99 ± 9.79 mm Hg (range: 9.5-60 mm Hg). Secondary glaucoma was diagnosed in 30 eyes of 15 patients (46.2%), and glaucoma suspicion was noted in 6 eyes of 3 patients (9.2%) based on clinical findings, such as borderline intraocular pressure and a somewhat increased optic nerve head excavation on ultrasound examination. Ultrasound B-scan examination demonstrated excavated glaucomatous cupping in 23 eyes of 13 patients (35.4%).

Regarding iris morphology, subtle pigment epithelial protrusion at the pupillary margin or a slightly displaced pupil due to iris frilling was observed in 8 eyes of 4 patients (12.3%), corresponding to grade 0. Atypical iris coloboma was found in 10 eyes of 5 patients (15.4%) (grade 1). Partial aniridia with more than six clock hours of residual iris tissue was noted in 16 eyes of 8

patients (24.6%) (grade 2), and less than six clock hours in 4 eyes of 2 patients (6.1%) (grade 3). Complete aniridia (grade 4) was observed in 25 eyes of 13 patients (38.5%)(**Figure 1**)(1,6).

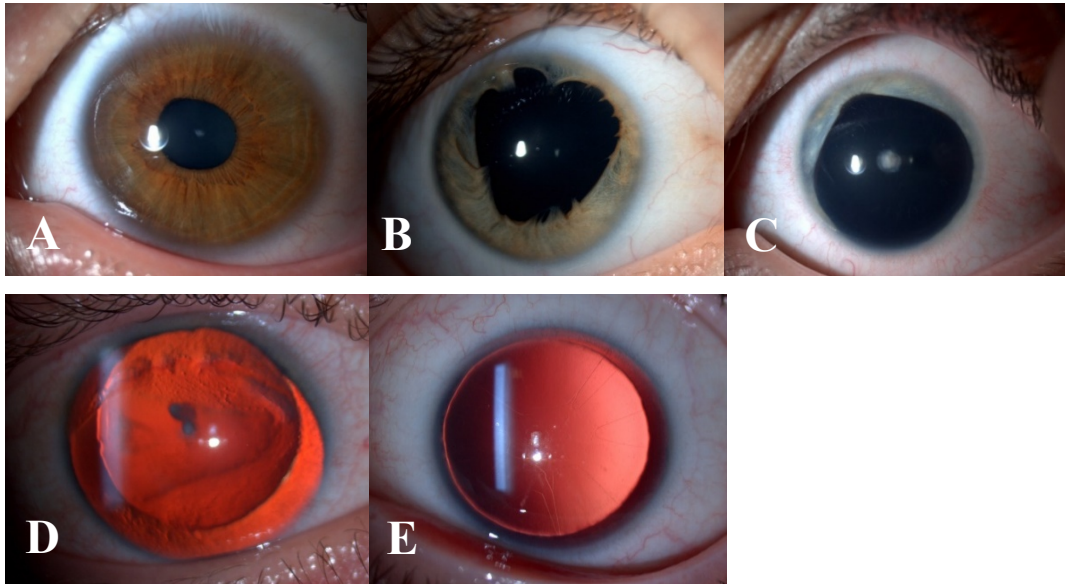


Figure 1. Various types of iris malformations observed in congenital aniridia. In (A), a slight outward bending of the pigment epithelium along the pupillary margin and a mildly displaced pupil are visible, corresponding to Grade 0. Image (B) shows an atypical iris coloboma (Grade 1). In (C), residual iris tissue extending over more than six clock hours is seen (Grade 2), while (D) depicts iris remnants covering less than six clock hours (Grade 3). Finally, (E) illustrates complete aniridia with total absence of the iris (Grade 4). Adapted from Náray et al. (1).

Regarding lens status, 8 eyes (12.3%) had a clear lens, while 22 eyes (33.8%) presented with anterior polar cataract and 24 eyes (36.9%) with cortical cataract (**Figures 2A and 2B**). Nuclear cataract was identified in 2 eyes (3.1%), and posterior polar cataract in 18 eyes (27.7%). A total of 13 eyes (20.0%) had previously undergone cataract surgery and were therefore pseudophakic (PCL). Additionally, 7 eyes (10.8%) demonstrated lens subluxation and/or zonular insufficiency (**Figure 2C**). Optic disc developmental abnormalities were confirmed in 2 eyes (3.0%) of 1 patient, while foveal hypoplasia (**Figure 3**) was detected in 6 eyes (4.6%) of 3 patients. In several cases, however, detailed slit-lamp and fundus examination was limited due to nystagmus and/or corneal and lenticular opacities, which hindered adequate visualization of the posterior segment (1).

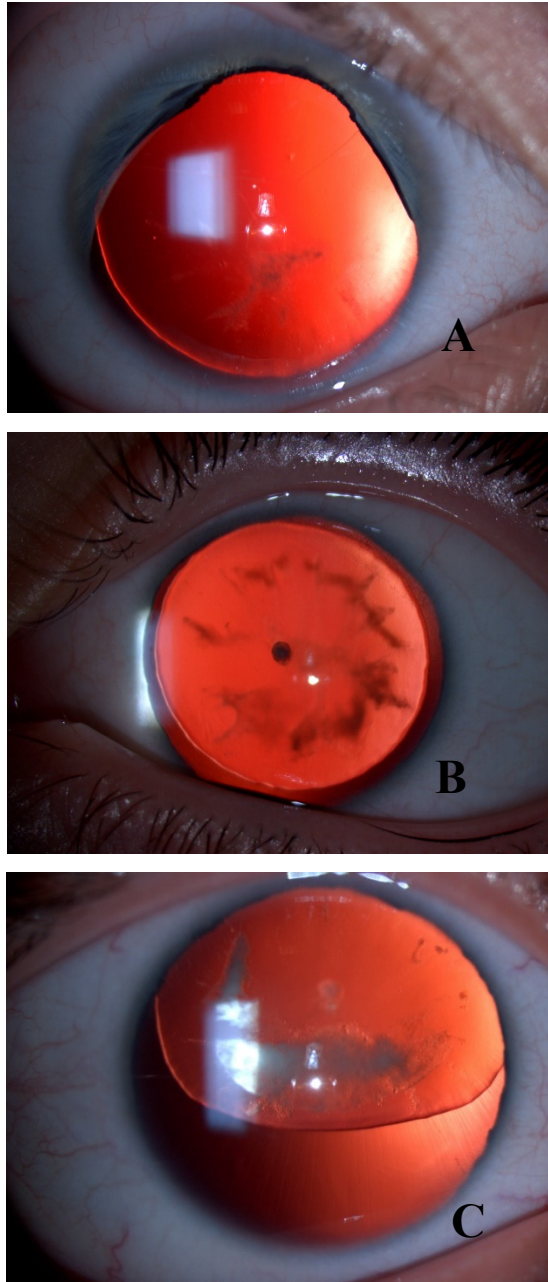


Figure 2. Cataract phenotypes in congenital aniridia, showing a posterior cortical opacity (A), an anterior polar opacity with peripheral cortical involvement (B), and a cortical opacity with lens subluxation (C). Adapted from Náray et al. (1).

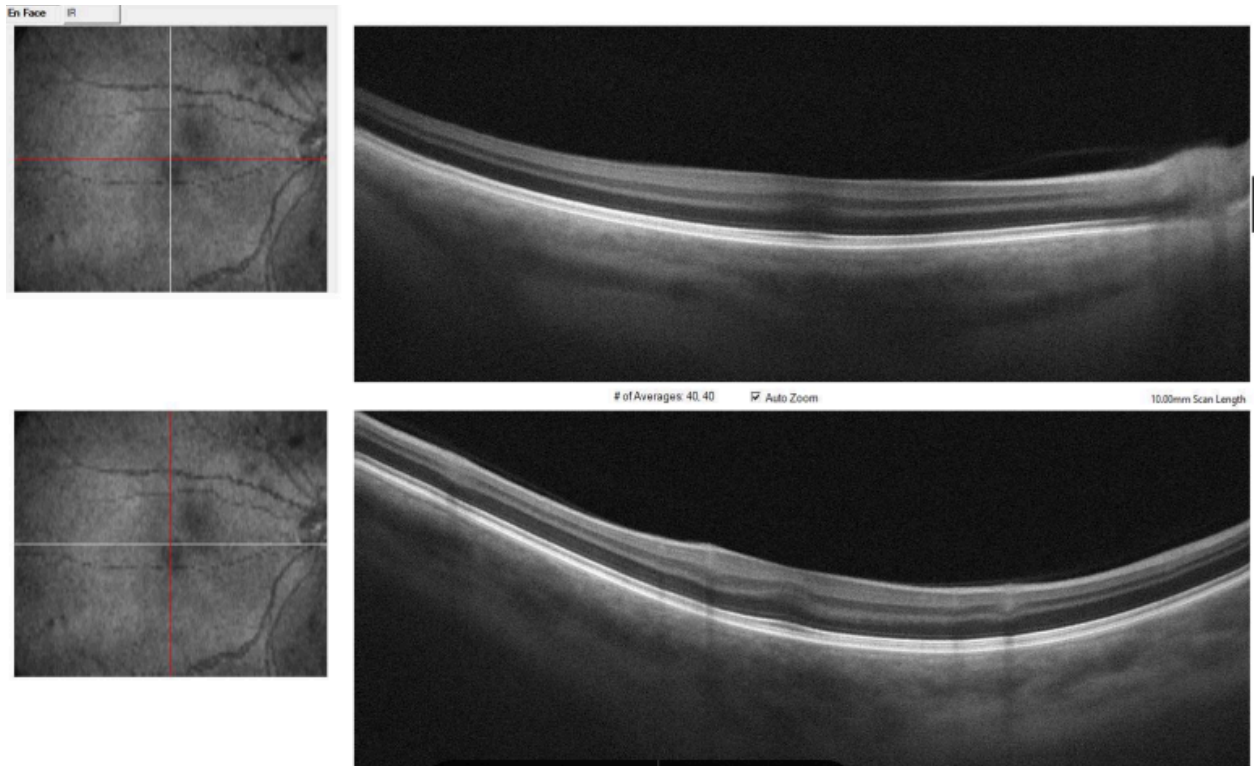


Figure 3. Foveal hypoplasia in congenital aniridia. Although no manifest iris malformation was visible in this pediatric patient (Leicester grade 2), the foveal hypoplasia observed on optical coherence tomography (OCT) clearly demonstrates that the posterior segment is also affected in PAX6-associated syndromes (1,26).

Systemic comorbidities were observed in several patients with CA. Hypertension occurred in 15.15% of cases, while metabolic disorders such as insulin resistance and diabetes mellitus were each detected in 3.03%. Thyroid dysfunction was present in one patient. Regarding BMI, 51.61% had normal weight, 25.8% were obese, and 12.9% overweight. Other chronic conditions included atopic dermatitis, asthma, viral hepatitis B, anaemia, polydactyly, and ADHD (each 3.03%). Over one-third (36.36%) of patients were on systemic medication, and more than half (54.84%) had a history of surgery, most commonly adenectomy and cholecystectomy. No renal, urogenital, or WAGR-associated abnormalities were identified. Although no hearing impairment or intellectual disability was recorded, mood instability was reported in nearly half of the cohort (45.16%), indicating potential neuropsychiatric involvement in CA. (Table 2)(1).

<i>Ophthalmological history in congenital aniridia patients (patients)</i>	
<i>familiar aniridia</i>	23 (69,7%)
<i>ptosis</i>	17 (51,52%)
<i>dry eye disease</i>	3 (4,6%)
<i>eye drops applied</i>	17 (51,5%)
β-blocker	12 (36,36%)
carboanhydrase inhibitor	12 (36,36%)
alfa-agonist	2 (6,06%)
prostaglandin-analog	4 (12,12%)
antibiotics	1 (3,03%)
preservative free artificial tears	7 (21,21%)
could not name the applied eye drops	1 (3,03%)
<i>cornea disease and surgery</i>	
penetrating keratoplasty and amnionplasty due to aniridia associated keratopathy	1 (3,03%)
<i>cataract and cataract surgery</i>	10 (30,30%)
<i>glaucoma and anti-glaucoma surgery</i>	13 (39,39%)/ 2 (6,06%)
<i>other eye surgery</i>	2 (6,06%)
bilateral cataract surgery combined with artificial iris implantation	1 (3,03%)
unilateral enucleation	1 (3,03%)
<i>use of therapeutic contact lenses</i>	4 (12,12%)
<i>Using visually impaired aids</i>	8 (24,24%)

Table 1. Ophthalmological history in patients with congenital aniridia. Adapted from Náráy et al.(1).

<i>Systemic history in congenital aniridia</i>	
<i>hypertension</i>	5 (15,15%)
<i>carbohydrate metabolism</i>	
insulin resistance	1 (3,03%)
diabetes mellitus	1 (3,03%)
<i>thyreoid malfunction</i>	1 (3,03%)
<i>body mass index (BMI)</i>	
underweight	3 (9,67%)
healthy weight	16 (51,61%)
overweight	4 (12,9%)
obese	8 (25,8%)
<i>renal pathology</i>	-
<i>urogenital malformation</i>	-
<i>WAGR syndrome</i>	-
<i>other chronic diseases</i>	11 (33,3%)
atopic dermatitis	2 (6,06%)
asthma bronciale	1 (3,03%)
viral hepatitis (HBV).	1 (3,03%)
iron deficiency anaemia	1 (3,03%)
polidactyly	1 (3,03%)
ADHD	1 (3,03%)
Medications	12 (36,36%)
acetazolamide	2 (6,06%)
amlodipin	1 (3,03%)
chlorthalidon	1 (3,03%)
subcutan insulin	1 (3,03%)
levothyroxine	1 (3,03%)
ciclesonide (inhalation)	1 (3,03%)
antiviral therapy (HBV)	1 (3,03%)
pantoprazol	1 (3,03%)
iron, vitamin V	1 (3,03%)

<i>previous chemotherapy</i>	-
<i>previous kidney surgery</i>	-
<i>other previous surgeries</i>	17 (54,84%)
adenectomy	5 (15,15%)
cholecystectomy	3 (9,09%)
phimosis	2 (6,06%)
umbilical hernia repair	2 (6,06%)
partial gastrectomy (perforated ulcer)	1 (3,03%)
hemorrhoid surgery	1 (3,03%)
papilloma excision.	1 (3,03%)
breast enhancement	1 (3,03%)
cervical conization	1 (3,03%)
caeserean section	1 (3,03%)
abscess extraction	1 (3,03%)
bilateral inguinal hernia	1 (3,03%)
appendectomy	1 (3,03%)
craniosynostosis surgery	1 (3,03%)
<i>hearing impairment</i>	-
<i>mood swings</i>	14 (45,16%)
<i>distemper</i>	14 (45,16%)
<i>mental retardation</i>	-

Table 2. Systemic history in patients with congenital aniridia. Adapted from Náray et al. (1).

In the German cohort 337 patients (mean age 22 ± 20 [0.3–90] years; 181 women [53.7%]) were included. Systemic pathologies were detected in 55 (46%) patients, among these obesity was the most prevalent in 29 (8.6%) patients, further identified diseases were thyroid disorder in 28 (8.3%) patients, arterial hypertension in 26 (7.7%) patients, intellectual disability in (22 6.5%) patients, diabetes mellitus in 19 (5.6%) patients, auditory processing disorder or language development delay in 16 (4.7%) patients, and epilepsy in 12 (3.6%) patients. Regarding the metabolic status of this patient population, in 14 cases (4.1%) metabolic syndrome described by increased waist circumference, arterial hypertension, elevated fasting blood glucose, abnormal

triglyceride levels, and high-density lipoprotein cholesterol levels, were discovered. Neurological comorbidities were also associated with congenital aniridia: structural central nervous system alterations were found in 8 (2.3%) patients, depression in 6 (1.8%) patients, and autism in 3 (0.9%) patients. Syndromic cases of congenital aniridia were also found such as WAGRO syndrome in 20 (10.7%) patients, Axenfeld-Rieger anomaly in one patient (0.3%) and Gillespie syndrome in one (0.3%) patient (16).

4.2. Examination of the stages of aniridia associated keratopathy in congenital aniridia in a Hungarian cohort

The 65 eyes of the 33 examined patients were classified according to the four established AAK staging systems. Based on *Mackman's* classification, 8 eyes (12.3%) were assigned to Stage 0, none to Stage 1A, 38 eyes (58.46%) to Stage 1B, and 19 eyes (29.23%) to Stage 2.

According to *Mayer's* system, 8 eyes (12.3%) were categorized as Stage 1, 38 eyes (58.46%) as Stage 2, 5 eyes (7.7%) as Stage 3, 7 eyes (10.77%) as Stage 4, and 7 eyes (10.77%) as Stage 5. Using *López-García's* classification, 8 eyes (12.3%) could not be categorized, while 20 eyes (30.77%) were classified as Stage 1, 18 eyes (27.7%) as Stage 2, and 19 eyes (29.3%) as Stage 3. Finally, following *Lagali's grading*, 8 eyes (12.3%) were in Grade 0, 20 eyes (30.77%) in Grade 1, 18 eyes (27.7%) in Grade 2, 5 eyes (7.7%) in Grade 3, and 14 eyes (21.54%) in Grade 4 (**Figures 4 and 5**) (20).

Mackman(21)	0	1A	1B	2		
	8 (12,3%)	0 (0%)	38 (58,46%)	19 (29,23%)		
Mayer(24)		I	II	III	IV	V
		8 (12,3%)	38 (58,46%)	5 (7,7%)	7 (10,77%)	7 (10,77%)
Lopez- García(22)	nincs beosztás	1	2	3		
	8 (12,3%)	20 (30,77%)	18 (27,7%)	19 (29,3%)		
Lagali(18)	0	1	2	3		4
	8 (12,3%)	20 (30,77%)	18 (27,7%)	5 (7,7%)		14 (21,54%)

Table 3. The examined patients were classified according to the different staging systems previously described in the literature.

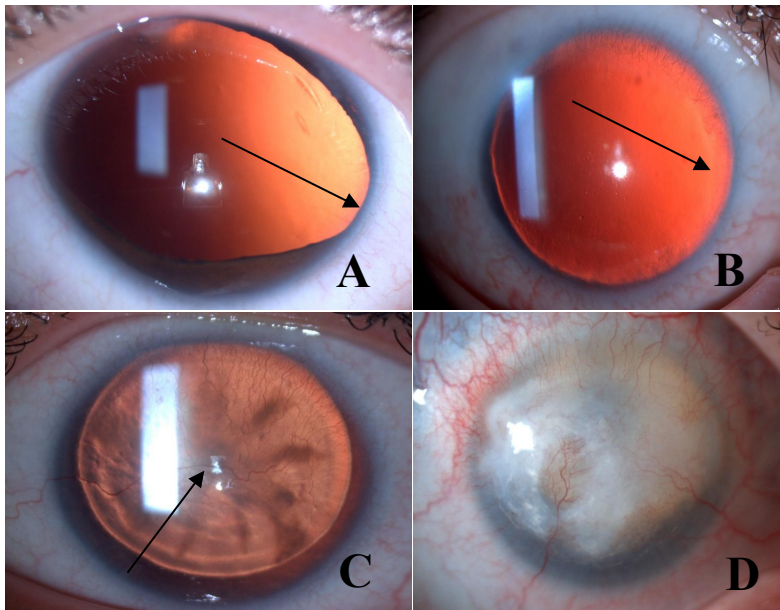


Figure 4. The staging of aniridia associated keratopathy according to Lagali [6]. In Grade 1 the conjunctiva and the vessels cross the limbus with 1 mm. (A). In case the conjunctiva and the vessels further approach the central cornea, but the central 2-3mm is intact, grade 2 is used. (B). When the vessels reach the central cornea grade 3 (C), then opaque, thick, corneal pannus grade 4 (D). Adapted from Náráay et al. (20).

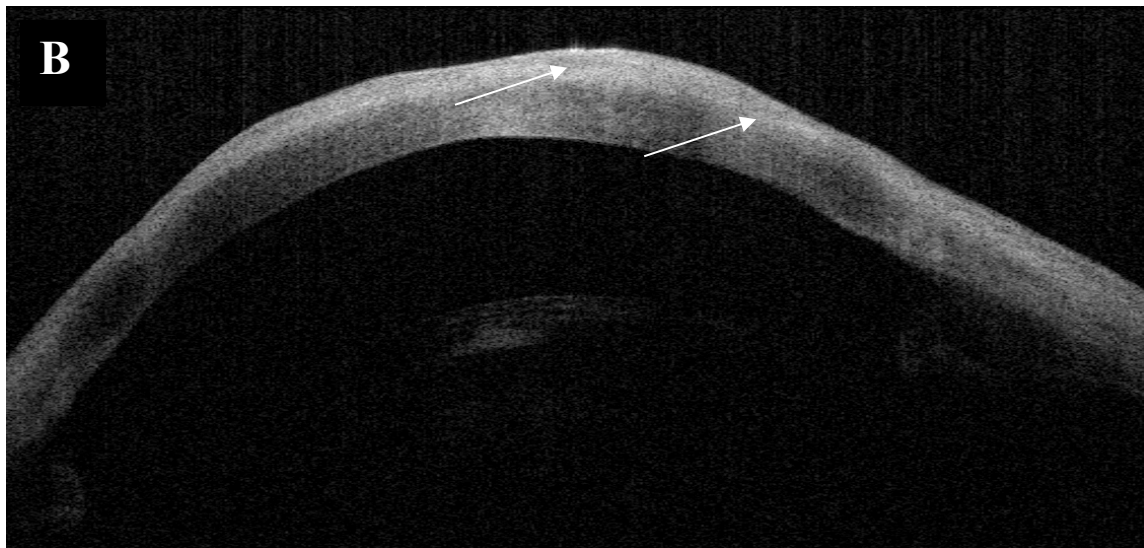
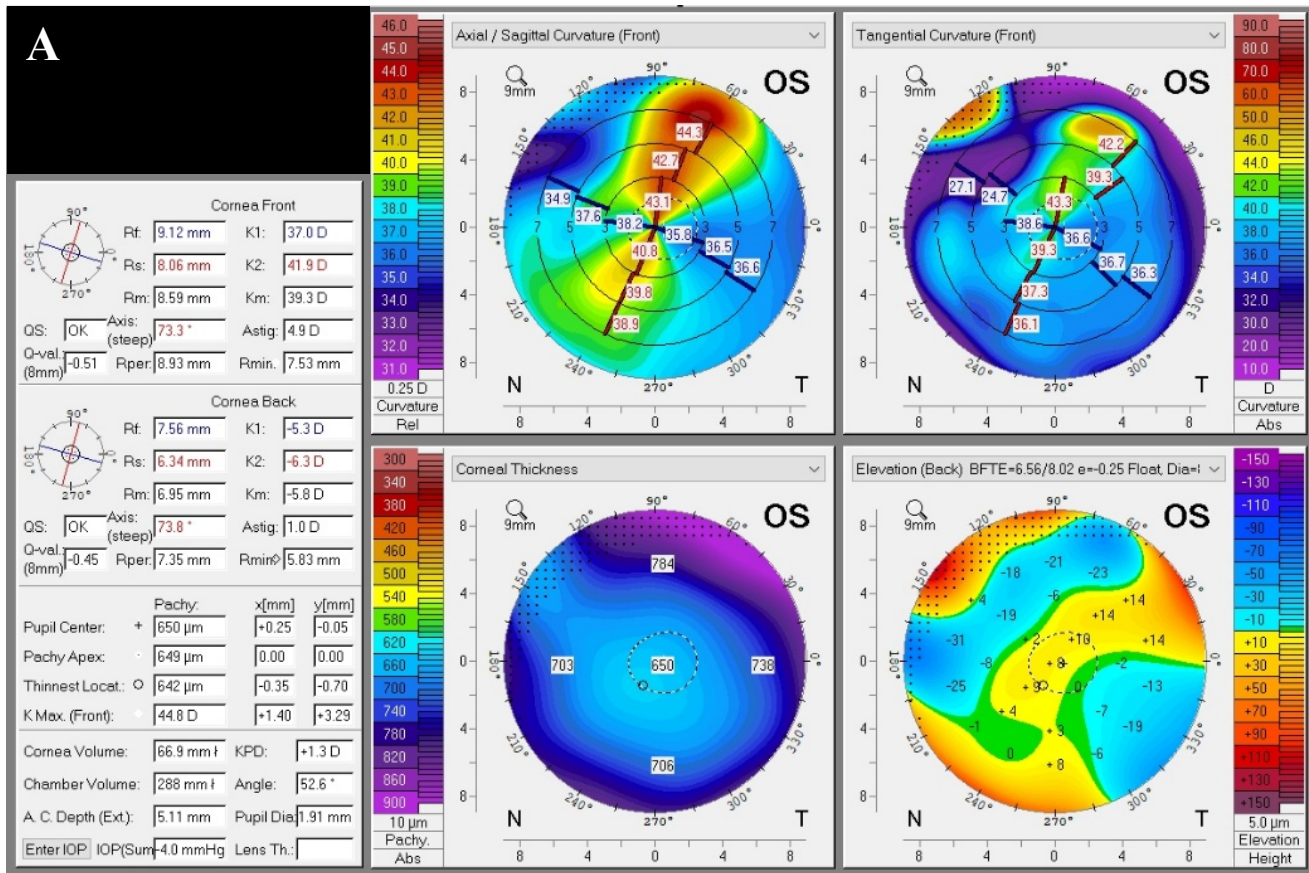


Figure 5. Aniridia-associated keratopathy (Lagali Grade 4). Corneal tomography (Pentacam-HR, Oculus, Wetzlar, Germany) and anterior segment OCT (Casia-I, Tomey, Erlangen-Tennenlohe, Germany) images demonstrate advanced corneal changes. The corneal surface appears markedly irregular (A), while the epithelial thickness is uneven (B, arrows). Both modalities reveal a globally thickened and structurally irregular cornea (A, B)(20)

4.3.Effect of lens properties on VA, stages of aniridia associated keratopathy and glaucoma: data from the Homburg Aniridia Centre

A total of 553 eyes from 286 patients were included in the Homburg Aniridia Center database. The mean age of participants was 19.9 ± 19.9 years (range: 0-83 years), comprising 255 males (46.1%) and 298 females (53.9%). In 19 subjects (6.6%), a total of 19 eyes had been previously enucleated and were therefore excluded from further analysis due to the lack of clinical information (25).

Mean VA was 1.2 ± 0.7 logMAR (range: -0.18 - 4.00), and VA could be determined in 467 eyes (84.4%). Based on Lagali's classification, 96 eyes (17.4%) were graded as Stage 0 AAK, 176 (31.8%) as Stage 1, 107 (19.3%) as Stage 2, 67 (12.1%) as Stage 3, and 107 (19.3%) as Stage 4. Mean IOP was 17.0 ± 6.9 mmHg (range: 2-50 mmHg), measurable in 492 eyes (89.0%)-using Goldmann applanation tonometry in 169 eyes (34.3%), iCare in 323 eyes (65.6%), and other methods in 22 eyes (4.4%). According to our glaucoma definition, 337 eyes (60.9%) met the diagnostic criteria for glaucoma.

Regarding lens status, 127 eyes (23.0%) had a clear lens, 223 (40.3%) exhibited cataract, 129 (23.3%) were pseudophakic, 32 (5.8%) were aphakic, and 10 (1.8%) had a subluxated lens. In 32 eyes (5.4%), the lens condition could not be assessed, primarily due to advanced corneal opacity. Within the pseudophakic subgroup, a posterior chamber lens was positioned in the capsular bag in 84 eyes (65.1%), and in the ciliary sulcus in 2 eyes (1.55%). Additionally, 32 eyes (24.8%) had undergone Morcher intraocular lens (IOL) implantation, 13 eyes (10.0%) received an artificial iris combined with IOL implantation, and 1 eye (0.7%) had a capsular tension ring (CTR) supporting the IOL. Retinal scars were observed in 5 eyes (0.9%), although no cases of AFS were identified in the cohort.

Lens status had a significant effect on both mean VA and IOP (ANOVA: $p < 0.0001$ and $p = 0.001$, respectively). Moreover, lens status showed a highly significant association with both AAK grade and the presence of glaucoma (Chi-square: $p < 0.0001$ for both). VA was significantly lower in eyes with cataract, pseudophakia, or aphakia compared with clear-lens eyes ($p < 0.001$ for all). Additionally, VA was significantly worse in pseudophakic and aphakic eyes than in cataract eyes ($p < 0.001$ and $p = 0.009$, respectively). A further difference was observed between pseudophakic/aphakic and subluxated-lens eyes, with poorer vision in the former ($p < 0.001$ for

both). Mean IOP was significantly lower in aphakic eyes compared to clear-lens, cataract, pseudophakic, and subluxated-lens eyes ($p=0.01$, $p<0.001$, $p=0.003$, and $p=0.01$, respectively). The most advanced AAK stages were found in pseudophakic and aphakic eyes, while glaucoma occurred more frequently in pseudophakic, aphakic, and subluxated-lens eyes.

To minimize potential age-related bias, VA (logMAR) was analyzed using a generalized linear model (GLM) with age as a covariate. The model ($R^2=0.242$) revealed a statistically significant difference in VA among the different lens categories ($p\leq0.001$). A similar GLM was applied to analyze IOP across lens categories, again controlling for age. Although this model yielded a lower R^2 value (0.041), indicating a smaller effect size, it still demonstrated a significant difference between groups ($p\leq0.01$), with aphakic eyes showing lower IOP on average than the other categories.

Using the Kruskal–Wallis test, followed by a Chi-square test, age was found to have a highly significant effect on lens status ($p<0.001$). To further clarify these associations, eyes were divided into age subgroups: 0–10 years (245 eyes, 44.3%), 10–20 years (84 eyes, 15.2%), 20–40 years (117 eyes, 21.2%), and 40+ years (97 eyes, 17.5%). Within these age groups, AAK stage remained strongly associated with lens status, in the 0–10 years ($p<0.001$), 10–20 years ($p<0.001$), and 40+ years ($p=0.02$) subgroups. Similarly, glaucoma presence was significantly linked to lens status, in the 0–10 years ($p=0.003$) and 20–40 years ($p=0.002$) groups. Across all subgroups, pseudophakic and aphakic eyes exhibited the most advanced AAK stages, while glaucoma occurred most frequently in pseudophakic, aphakic, and subluxated-lens eyes (25).

5. Discussion

5.1. Examination of ocular and systemic comorbidities in congenital aniridia: data from Hungary and Germany

Aniridia is a complex congenital disorder affecting the entire eye, named for the characteristic hypoplasia of the iris. The degree of iris underdevelopment can vary widely—from a complete absence of the iris, through coloboma-like defects, to subtle irregularities of the pupillary margin that may only be detected by detailed slit-lamp examination. The impact of the disease on vision is also highly variable. In many cases, it causes severe congenital visual impairment leading to abnormal visual development and nystagmus (27–30). In our cohort, approximately 70% of patients exhibited nystagmus, with a mean uncorrected visual acuity of 0.14 (1).

Congenital aniridia can be divided into *PAX6*-associated and non-*PAX6*-associated forms. Certain ocular complications are more common in the *PAX6*-related type. *PAX6*-associated aniridia may present as an isolated condition caused by inherited or de novo mutations in the *PAX6* gene, or as part of syndromic forms such as WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability) or WAGRO syndrome (WAGR with obesity). Recent evidence indicates that even so-called “isolated” *PAX6* aniridia often involves systemic manifestations—hormonal, gastrointestinal, metabolic, or neurological—supporting the term “aniridia syndrome” or “*PAX6* syndrome,” as proposed by Käsmann-Kellner (4,27–31). In our study, we also examined the presence of systemic diseases based on patient history. Hypertension was reported in 5 cases (15.15%) in the Hungarian cohort, while other systemic disorders were not frequent. However, 14 patients (45.16%) reported mood fluctuations, highlighting the need for further investigations to uncover potentially undiagnosed systemic comorbidities (1).

In the German cohort, chronic systemic diseases were the most prevalent such as obesity in 29 (8.6%) patients, thyroid disorder in 28 (8.3%) patients, arterial hypertension in 26 (7.7%) subjects. The presence of these chronic comorbidities underline the importance of regular comprehensive medical examinations within the congenital aniridia patient population, which can lead to timely detection and effective treatment.(16)

Iris malformation is the hallmark of the aniridia phenotype. Depending on the *PAX6* pathogenic variant, the iris may range from completely absent to slightly displaced

(corectopia) or show atypical coloboma-like defects (18,32,33). This structural abnormality contributes to the pronounced photophobia characteristic of the condition. In our cohort, all morphological grades of iris malformation (grade 0-grade 4) were observed, underscoring the spectrum nature of congenital aniridia. Increasing severity of iris hypoplasia was typically associated with more advanced AAK and greater lens abnormalities (1).

AAK develops in up to 80% of patients with *PAX6*-related aniridia over time and results from multiple interacting factors. In our study, AAK was present in 57 eyes (87.7%). The limbal stem cells (LSCs) are essential for corneal epithelial regeneration and for maintaining the corneal-conjunctival epithelial boundary. AAK partly results from limbal stem cell deficiency (LSCD) due to *PAX6* pathogenic variants, compounded by secondary factors such as dry eye disease, impaired epithelial differentiation and adhesion, and abnormal wound healing (18,28). Clinical signs often appear early in life, initially as peripheral epithelial thickening. By the second decade, chronic irritation and superficial vascularization develop at the limbus, gradually extending toward the central cornea. In later stages, progressive pannus formation and stromal vascularization lead to central corneal involvement, scarring, and vision loss (18,28,33). Despite these findings, 90.9% of our patients had normal OSDI scores, and no cases of severe dry eye were detected, suggesting that the evolution of ocular surface disease in aniridia requires further longitudinal study (1).

Cataract occurs in 50–85% of patients with aniridia (18,32,33). In our series, 57 eyes (87.7%) were affected or had undergone cataract surgery. The most frequent types were anterior polar cataract (22 eyes, 33.84%) and posterior polar cataract (18 eyes, 27.69%). Some patients exhibited progressive cataract variants. Lens subluxation was observed in 7 eyes (10.77%) due to zonular weakness or defects. In certain cases, lens extraction and intraocular lens implantation were required to improve vision, although surgical intervention carries a significant risk of rapid worsening of AAK and aniridia fibrosis syndrome postoperatively (1,27–31,34).

AFS is a progressive anterior segment fibrosis disorder characterized by the formation of an inflammatory membrane between the residual iris strands, which may extend toward the posterior segment and involve the ciliary body. As a result, ocular hypotony and retinal detachment can develop (28,30,35). Within our cohort, no patient received the diagnosis of AFS, however one patient had undergone enucleation on one of his eye that had previously undergone cataract surgery, and cornea transplantation. (1)

Secondary glaucoma occurs in 6–75% of cases and often presents before adulthood. In our study, glaucoma was confirmed in 30 eyes (46.15%) of 15 patients, while 6 eyes (9.2%) in 3 patients were classified as glaucoma suspects. The condition is typically caused by abnormal aqueous outflow due to a malpositioned Schlemm's canal and rudimentary iris tissue obstructing the trabecular meshwork (27,29,30). Regular monitoring of intraocular pressure and optic nerve head morphology is essential for early diagnosis occasionally supplemented by visual evoked potential (VEP) testing (36). However, nystagmus and keratopathy can complicate fundus evaluation. Secondary glaucoma remains the most serious sight-threatening complication, often leading to irreversible visual loss or blindness.

Optic disc and foveal hypoplasia are frequent findings in aniridia (81-91%), although foveal hypoplasia can occur independently of optic nerve underdevelopment (37). In our cohort, optic disc anomalies were detected in 2 eyes (3.03%) of 1 patient, and foveal hypoplasia in 6 eyes (4.6%) of 3 patients (1,2)

In summary, the principal ophthalmic manifestations of congenital aniridia include aniridia-associated keratopathy, secondary glaucoma, cataract, and foveal and optic nerve hypoplasia. Prevention, treatment, and long-term management of these complications require the lifelong, coordinated care of multiple ophthalmic subspecialties (37).

5.2. Examination of the stages of aniridia associated keratopathy in congenital aniridia in a Hungarian cohort

Since the first description AAK, a growing body of clinical evidence has expanded our understanding of its development and progression. This accumulation of data has led to the need for a more comprehensive and standardized clinical staging system, which facilitates both the characterization of disease severity and the optimization of patient management (8,18–24).

Although the pathogenesis of AAK has not yet been fully elucidated, significant refinements in its classification have occurred between 1979 and 2020. The early Mackman system primarily focused on the initial appearance and peripheral spread of keratopathy, followed by central involvement, but did not include corneal staining or quantify the stepwise central extension of the pathology (21). Later, Mayer's classification incorporated fluorescein staining for stage differentiation and identified the formation of thick pannus as a key feature (20,23,24).

In contrast, López-García proposed a staging method that precisely defined limbal involvement (>1 mm) and included parameters such as epithelial erosions, ulcers, subepithelial opacities, and subjective patient symptoms. However, this system is partly limited by the lack of objective evaluation of patient-reported complaints and the possible absence of detailed medical documentation regarding previous corneal lesions (20,22).

The Lagali classification, introduced more recently, describes AAK progression using millimetre-based measurements from the periphery toward the centre and adds an advanced stage for cases with a dense, opaque central pannus (18–20).

Approximately nine out of ten patients with aniridia carry a *PAX6* haploinsufficiency. The *PAX6* gene is crucial for early eye morphogenesis and remains active in various ocular tissues throughout life. The specific genetic background of congenital aniridia largely determines the severity and course of AAK. Interestingly, variants confined to non-coding regions of *PAX6* are often associated with milder forms of keratopathy that rarely progress beyond grade 1, even after long-term follow-up. Therefore, genetic testing and mutation analysis are essential for prognostic assessment and patient counselling. In addition to genetic alterations, epigenetic influences are also believed to contribute significantly to the development and variability of AAK (8,18,20).

In early-stage disease (grades 1–2), patients may experience ocular dryness, recurrent epithelial erosions, or ulceration. Management at this stage is typically conservative, relying on preservative-free lubricants, autologous serum eye drops, and therapeutic soft contact lenses (18–20,22,23).

In more advanced stages (grades 3–4), pannus removal (pannectomy) and amniotic membrane transplantation (AMT) may be indicated, often combined with intensive topical therapy, including autologous serum and, when needed, lateral tarsorrhaphy to promote epithelial healing (20,28,38).

Because the underlying cause of AAK is limbal stem cell deficiency, the restoration of vision and the ocular surface ideally requires limbal stem cell transplantation. Unfortunately, even with HLA (human leukocyte antigen) matching, long-term outcomes have been disappointing, with limited or no functional recovery (39,40). When stromal scarring becomes prominent, penetrating keratoplasty may be considered, although its success strongly depends on the integrity of the limbal stem cell population (18,19,23,40,41). In selected cases, keratoprosthesis implantation has yielded more favourable and sustained visual outcomes in congenital aniridia (18–20).

It is also important to note that meibomian gland dysfunction (MGD) and tear film instability frequently coexist with AAK, and their severity often correlates with the degree of corneal involvement. Consequently, effective treatment of MGD, along with tear supplementation, is a critical component of comprehensive therapy (8,20).

To gain deeper insight into the molecular mechanisms underlying AAK, several experimental studies have been conducted. Latta and colleagues identified altered microRNA expression in conjunctival cells from aniridia patients and reported changes in retinol metabolism within limbal epithelial cells, specifically reduced expression of ADH7 and ALDH1A1 (20,41).

Given the challenges of studying primary cells from a rare disease, the same group developed an in vitro cell model to explore gene expression changes after *PAX6* knockdown in limbal epithelial cells (41). Using this system, they demonstrated decreased expression of *DSG1* and *FABP5* following *PAX6* suppression (20,32,42).

The limbal stem cell niche, composed of both cellular and extracellular components, provides the specialized microenvironment necessary for maintaining stem cell function. Schlötzer-Schrehardt et al. examined this niche in congenital aniridia and observed degeneration of Vogt's palisades and the basement membrane, accompanied by epithelial thinning, hyperplasia, and inflammatory infiltration (43). Further investigations are needed to clarify the mechanisms driving LSCD and its progression in this disease (20).

In conclusion, the Lagali staging system offers the most practical and detailed approach for assessing aniridia-associated keratopathy. It allows for straightforward documentation, accurate monitoring of disease progression, and supports both prognostic evaluation and treatment planning. The diagnosis, follow-up, and management of patients with AAK should be centralized in specialized tertiary centres equipped with multidisciplinary expertise in congenital aniridia care (20).

5.3. Examination of the effect of lens surgery in patients with congenital aniridia: data from the Homburg Aniridia Centre

Congenital aniridia is a panocular disorder characterized by a broad range of ocular abnormalities, among which iris hypoplasia, AAK, foveal and optic nerve head hypoplasia, and both congenital and age-related cataract are the most frequent manifestations, reported in up to 90% of affected eyes (5,44). In a cohort of 94 patients with congenital aniridia, Jacobson et al. found no significant difference in BCVA between phakic and pseudophakic eyes (5). However, to date, large-scale analyses evaluating postoperative visual outcomes, AAK progression, and glaucoma incidence after cataract surgery in aniridia have been lacking (25).

In the current study, lens status demonstrated a strong influence on VA and IOP. Mean VA was markedly reduced in eyes with cataract, pseudophakia, or aphakia compared with clear-lens eyes, and was lowest in pseudophakic and aphakic eyes. Similar trends were observed for AAK severity and the prevalence of glaucoma. Interestingly, eyes that underwent Morcher IOL or artificial iris implantation showed higher AAK grades and a higher incidence of glaucoma compared with eyes that received standard in-the-bag IOL implantation (25).

Previous reports on cataract surgery in aniridia are limited. Wang et al. described 17 eyes of 10 patients (mean age 25.4 ± 14.7 years) undergoing phacoemulsification with capsular tension ring (CTR) and posterior chamber lens implantation. Over a mean follow-up of 10.2 ± 6.4 months, neither corneal deterioration nor secondary glaucoma was observed (45). In contrast, Reinhardt et al. retrospectively analyzed 19 eyes of 14 patients receiving iris–lens diaphragm (ILD) implantation in the ciliary sulcus. Although BCVA improved in 73% of eyes, 37% showed corneal worsening and 42% developed or exhibited progression of glaucoma over a mean 46-month follow-up (46).

In our large cohort of 553 eyes, most pseudophakic eyes (84 eyes, 65.1%) had posterior chamber IOLs placed in the capsular bag, while only 2 eyes (1.5%) had sulcus fixation. Morcher IOLs were implanted in 32 eyes (24.8%), artificial iris combined with IOLs in 13 eyes (10.0%), and CTR-supplemented IOLs in 1 eye (0.7%). Because many surgeries had been performed years earlier at other institutions, postoperative follow-up intervals could not be precisely determined, though they were likely longer than those reported by Wang and Reinhardt (25,45,46).

A key question arising from our findings is why eyes that have undergone intraocular surgery often show more advanced AAK and higher rates of secondary glaucoma. To unravel these mechanisms, close collaboration between clinical and basic researchers is essential. Chronic ocular surface inflammation and progressive limbal stem cell deficiency (LSCD) are known hallmarks of AAK, even without prior intraocular surgery (8, 16). Furthermore, the *PAX6* gene, a master transcriptional regulator in ocular development, modulates numerous downstream targets whose dysregulation due to *PAX6* haploinsufficiency—further influenced by genotype-specific and epigenetic factors—may drive disease progression (8, 16). Among these, *FOSL2* and *FABP5* are of particular interest as potential molecular mediators (31, 46). Understanding how these genetic pathways interact with surgical trauma and inflammatory signaling may clarify the mechanisms behind postoperative deterioration.

Both AAK severity and glaucoma frequency typically increase with age in congenital aniridia. Using generalized linear modelling with age as a covariate, we confirmed a significant impact of lens status on VA and IOP. However, since many patients were receiving antiglaucoma therapy, IOP may not fully reflect disease activity. When we analyzed age-stratified subgroups, cataract surgery remained significantly associated with worse AAK grades and higher glaucoma prevalence across multiple age brackets (0-10, 10-20, and >40 years). These results support the hypothesis that intraocular surgery may trigger inflammatory responses and structural alterations at the ocular surface and angle, contributing to disease progression. Additionally, lens subluxation itself was associated with secondary glaucoma development (25).

AFS is a serious postoperative complication characterized by progressive anterior segment fibrosis and formation of retrolenticular or retrocorneal membranes. Tsai et al. (2005) reported AFS in 4.5% of eyes (7 eyes of 6 patients) within a cohort of 155 eyes, with some cases extending posteriorly to the ciliary body and resulting in hypotony and retinal detachment (30). Wider sclerocorneal incisions required for Morcher or artificial iris implants appear to increase this risk (35). Figueiredo et al. observed AFS in 3.1% of eyes fitted with custom iris prostheses (48), and Romano et al. reported AAK worsening and glaucoma progression after artificial iris implantation (7, 25).

In our dataset, no definitive AFS cases were identified. However, five eyes (0.9%) showed retinal scarring, and nineteen eyes (6.6%) from enucleated patients could not be fully assessed; AFS cannot be ruled out in these excluded cases. The absence of confirmed AFS among the

analyzed eyes may reflect the predominance of in-the-bag IOL placement, the relatively small number of complex implantations (Morchers or artificial iris), and the limited number of repeat intraocular surgeries performed at our center. AFS likely arises from multifactorial mechanisms involving damage to the limbal stem cell niche, abnormal iris and ciliary structures, and developmental lens anomalies (43). Progressive AAK and secondary glaucoma may represent early indicators or risk factors for AFS onset. Therefore, advanced AAK and existing glaucoma should be regarded as relative contraindications for cataract surgery in congenital aniridia. Determining a safe surgical window with acceptable risk remains an important future goal.

Because congenital aniridia affects virtually all ocular structures, planning cataract surgery requires a comprehensive, multidisciplinary assessment of the ocular surface, limbal stem cell status, and glaucoma control (6, 8, 26). In early childhood, preventing amblyopia is a major priority (49), while VEP testing may aid in predicting potential visual improvement in older patients (50). Histopathological studies have revealed thinning of the lens capsule, complicating continuous curvilinear capsulorhexis formation, while absence of iris landmarks and zonular weakness or subluxation further increase surgical complexity (11, 50).

For these reasons, cataract surgery in aniridia should only be performed by experienced surgeons. Image-guided systems may assist in performing precise capsulorhexis. (51) Based on current evidence and our findings, if cataract extraction is necessary, the preferred option remains small-incision phacoemulsification with posterior chamber IOL placement in the capsular bag, avoiding CTRs, ILDs, or prosthetic iris devices (7, 34, 45, 47). Postoperatively, beside the standard topical corticosteroid and antibiotic treatment, frequent autologous serum eye drops are recommended to support limbal and corneal healing (28).

A better understanding of the molecular mechanisms driving postoperative AAK progression and secondary glaucoma could lead to new therapeutic strategies in congenital aniridia.

Our analysis included data from the first clinical examination of congenital aniridia patients at the Homburg Aniridia Center. A prospective longitudinal study with standardized pre- and postoperative follow-up would provide more detailed insight into the long-term course of visual function, ocular surface health, and glaucoma development after cataract surgery. Another limitation is the use of different tonometry techniques among patients, which prevented full standardization of IOP data. Additionally, office-based measurements, particularly in patients with nystagmus, may have affected measurement accuracy (25).

In summary, previous cataract surgery in congenital aniridia appears to be associated with worsening AAK severity and increased prevalence of secondary glaucoma in both pseudophakic and aphakic eyes. Lens subluxation may also predispose to glaucoma. These findings emphasize the need for careful preoperative evaluation and individualized risk-benefit assessment before considering cataract surgery in this patient population. Future research combining clinical observations with molecular investigations may clarify the mechanisms underlying postoperative AAK progression and glaucoma, ultimately guiding the development of targeted therapies for congenital aniridia (25).

6. Conclusions

The ophthalmic signs of congenital aniridia are the aniridia associated keratopathy, the secondary glaucoma, cataract, macula and opticus hypoplasia. To prevent certain ophthalmic complications, the cooperation of different ophthalmic subspecialties in care and follow up is crucial. Patients with congenital aniridia frequently present with systemic comorbidities, most notably hypertension, thyroid disorder, metabolic alterations, and obesity. The high rate of previous surgeries and frequent reports of mood instability underline the multisystemic and psychosocial impact of the disease. These findings emphasize the need for a multidisciplinary approach to patient care, incorporating systemic monitoring and psychological support alongside ophthalmic management.

When grading the aniridia associated keratopathy the system per Lagali is recommended, since the examination is easily feasible, along with documentation, the stages follow the progression appropriately, with this assisting in predicting the prognosis, and choosing a suitable therapy. The care and follow up of aniridia associated keratopathy should be managed in special centers.

In congenital aniridia, previous cataract surgery may be associated with progression of AAK severity and the presence of secondary glaucoma both in postoperatively pseudophakic and aphakic eyes. Subluxated lens may result in secondary glaucoma in congenital aniridia. Our data indicate that careful consideration is warranted before considering cataract surgery in congenital aniridia subjects. We anticipate that in the years ahead, the precise causes of these clinically observed phenomena will become more clear. Gaining insights into the molecular mechanisms responsible for the accelerated aniridia associated keratopathy and secondary glaucoma progression after intraocular surgery, could potentially unveil new therapeutic targets for congenital aniridia in the near future.

7. Summary

Congenital aniridia is a complex, multisystemic ocular disorder characterized by a constellation of ophthalmic manifestations, including AAK, secondary glaucoma, cataract, and foveal and optic nerve hypoplasia. The prevention and management of these complications require close collaboration among different ophthalmic subspecialties, ensuring comprehensive and long-term patient care. Overall, individuals with congenital aniridia often exhibit a range of systemic health issues, particularly hypertension, thyroid disorder, metabolic disturbances, and increased body weight. The notable frequency of previous surgical interventions and emotional instability reflects the broader systemic and psychological burden associated with the condition. These observations highlight the importance of a comprehensive, interdisciplinary care strategy, ensuring regular systemic evaluation and mental health support in addition to ophthalmological follow-up.

For the grading of AAK, the Lagali classification system is recommended, as it allows for straightforward clinical application and reliable documentation. The system reflects disease progression accurately, thereby supporting clinicians in establishing prognosis and selecting optimal therapeutic strategies. Patients with AAK should ideally be monitored and treated in specialized referral centers with expertise in aniridia and ocular surface disease.

Our findings further suggest that previous cataract surgery in congenital aniridia may contribute to the progression of AAK and an increased incidence of secondary glaucoma, particularly in pseudophakic and aphakic eyes. Additionally, lens subluxation appears to predispose patients to glaucoma development. These observations highlight the importance of careful surgical planning and individualized risk assessment before undertaking intraocular procedures in this vulnerable patient population.

Future research aimed at elucidating the molecular mechanisms underlying postoperative exacerbation of keratopathy and glaucoma may uncover novel therapeutic targets, ultimately improving long-term outcomes for individuals affected by congenital aniridia.

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