

OPHTHALMIC AND SYSTEMIC SIGNS OF CONGENITAL ANIRIDIA

PhD thesis

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1. Introduction

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. In approximately 90% of cases, the disease results from autosomal dominant pathogenic variants in the PAX6 gene, 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.

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.

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. 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.

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). In most cases, however, residual iris stumps can still be

visualized by gonioscopy. 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.

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. Tinted or colored contact lenses may alleviate photophobia; however, their use is frequently contraindicated in patients with advanced stages of keratopathy.

Aniridia associated keratopathy

AAK represents a distinct form of corneal disease characteristic of CA. The prevalence of AAK, at varying stages of severity, has been reported to reach approximately 80% among affected individuals. 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.

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.

Cataract

The prevalence of cataract in individuals with CA ranges between 40% and 80%, with many cases being congenital or appearing during the second decade of life. The most typical morphologic types are anterior and posterior polar cataracts. Although cataract surgery often results in temporary improvement of 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. These complications may include

the progression of AAK, the onset or worsening of glaucoma, and the development of the severe aniridia fibrosis syndrome (AFS), which in advanced cases may lead to phthisis bulbi.

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 using macular optical coherence tomography (OCT) or fundus autofluorescence (FAF) imaging, which typically reveals the absence of the foveal avascular zone. In affected children, the degree of foveal hypoplasia largely determines future VA.

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. Another, less frequent entity is Gillespie syndrome, which presents with bilateral aniridia and cerebellar ataxia.

Auditory deficits have also been reported in children with PAX6 mutations 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.

Experimental studies in murine models have revealed that PAX6 mutations 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.

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.

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. 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.

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. 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.

Cataract surgery in congenital aniridia

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%. 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.

Previous studies have reported conflicting outcomes regarding the efficacy and safety of cataract surgery in patients with CA. A serious postoperative complication, known as AFS, has been described in the literature, characterized by fibrotic transformation of the lens capsule following intraocular surgery, which in advanced cases may ultimately lead to phthisis bulbi. 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.

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. In the Hungarian cohort patients seen at the Department of Ophthalmology, Semmelweis University, between October 2005 and May 2022 were included. After obtaining each patient's medical history, a comprehensive ophthalmic evaluation was carried out. In the German cohort patients with congenital aniridia examined at the Department of Ophthalmology of Saarland University Medical Center, after June 2003 were included. The systemic anamnestic data were extracted from the medical records, into a database.

3.2. We assessed 65 eyes from 33 individuals diagnosed with congenital aniridia (mean age: 25.69 ± 17.49 years, range 5-59; 17 females, 51.51%). Corneal findings were documented using slit-lamp biomicroscopy, and corneal alterations were categorized according to the staging systems of Mackman, Mayer, López-García, and Lagali.

3.3 Participants with congenital aniridia examined at the Department of Ophthalmology, Saarland University, between June 2003 and January 2022 were included. Data from the initial visit -including visual acuity, slit-lamp results, AAK grading, and glaucoma assessment- were retrieved from medical records. Eyes were classified as having a clear lens, cataract, pseudophakia, aphakia, or lens subluxation. Patients were further divided into age groups (0-10, 10-20, 20-40, and over 40 years).

4. Results

4.1 In the Hungarian cohort among the 82 individuals listed in the database, 33 patients (mean age 25.69 ± 17.49 years, range 5-59; 17 women, 51.51%) attended for evaluation, and a total of 65 eyes were assessed. Nystagmus was observed in 45 eyes from 23 patients (69.23%). The mean uncorrected distance visual acuity was 0.14 ± 0.128 (0.9 logMAR; 0.63-0.005). Aniridia-associated keratopathy was graded as follows: Grade 0 in 8 eyes (12.3%), Grade 1 in 10 eyes (15.38%), Grade 2 in 16 eyes (24.62%), Grade 3 in 4 eyes (6.15%), and Grade 4 in 25 eyes (38.46%). Secondary glaucoma was present in 30 eyes (46.15%) of 15 patients, and 6 eyes (9.2%) from 3 patients were categorized as glaucoma suspects. Regarding lens status, 8 eyes (12.3%) had a transparent lens, while cataract was seen in 44 eyes (67.69%), including 22 anterior cortical polar cataracts (33.84%). Thirteen eyes (20%) were pseudophakic, and 7 eyes (10.77%) showed lens subluxation or zonular weakness. Macular hypoplasia was detected in 6 eyes of 3 patients (4.6%), and optic nerve head anomalies were identified in 2 eyes of 1 patient (3.03%). Regarding systemic involvement, 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%). 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.

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. 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 Using Mackman's grading system, 8 eyes (12.3%) were classified as stage 0, none as stage 1A, 38 eyes (58.46%) as stage 1B, and 19 eyes (29.23%) as stage 2. Based on Mayer's scheme, 8 eyes (12.3%) fell into stage I, 38 eyes (58.46%) into stage II, 5 eyes (7.7%) into stage III, while stages IV and V each included 7 eyes (10.77%). According to the López-García classification, 8 eyes (12.3%) could not be assigned to any category; 20 eyes (30.77%) were placed in stage 1, 18 eyes (27.7%) in stage 2, and 19 eyes (29.3%) in stage 3. Using Lagali's system, 8 eyes (12.3%) corresponded to stage 0, 20 eyes (30.77%) to stage 1, 18 eyes (27.7%) to stage 2, 5 eyes (7.7%) to stage 3, and 14 eyes (21.54%) to stage 4.

4.3 In a total of 553 eyes from 286 individuals with congenital aniridia (mean age 19.9 ± 19.9 years, range 0-83; 46.1% male), evaluation showed that both visual acuity and average intraocular pressure varied significantly depending on lens status (ANOVA $p < 0.0001$ and $p = 0.001$, respectively). Lens condition was also highly correlated with AAK grade and the presence of glaucoma ($p < 0.0001$ for both associations). When analyzing the predefined age categories, AAK stage demonstrated a strong relationship with lens status in the 0-10-year ($p < 0.001$), 10-20-year ($p < 0.001$), and 40+ year ($p = 0.02$) groups. Furthermore, lens status was significantly linked to glaucoma occurrence in the 0-10-year ($p = 0.003$) and 20-40-year ($p = 0.002$) groups. The most advanced AAK stages were observed in pseudophakic and aphakic eyes, and glaucoma was more frequently detected in eyes that were pseudophakic, aphakic, or had a subluxated lens.

5. Conclusions

5.1 Typical ocular manifestations of congenital aniridia include aniridia-associated keratopathy, secondary glaucoma, cataract, as well as hypoplasia of the macula and the optic nerve head. Effective management of these conditions requires coordinated input from multiple ophthalmic subspecialties. In addition, due to systemic comorbidities such as obesity, hypertension, thyroid disorder, regular comprehensive medical examination is advised for timely diagnosis and management. WAGR syndrome is a potentially life-threatening disease due to Wilms tumor, therefore a detailed pediatric examination is recommended upon diagnosis of congenital aniridia.

5.2 For assessing aniridia-associated keratopathy, we advise using the Lagali classification, as it is user-friendly and provides a clear depiction of disease progression that supports therapeutic decision-making. In Lagali stage 1, neovascularization extends up to 1 mm beyond the limbus; in stage 2, the central 2-3 mm of the cornea remain free of vessels. Once vessels reach the central cornea, the condition corresponds to stage 3, while stage 4 is defined by dense, irregular corneal pannus.

5.3 In a large cohort of patients with congenital aniridia, eyes that had undergone cataract surgery, resulting in either pseudophakia or aphakia, showed higher grades of AAK and a greater likelihood of secondary glaucoma. These findings suggest that cataract surgery should be approached with particular caution in this patient population.

6. Bibliography of the candidate's publications

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