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CASE REPORT

# Familial Congenital Aniridia with Subluxated Lens and Glaucoma

**Authors:**
Birgitta Henny Perwitasari*
Dicky Hermawan

**Affiliations:**
Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga – RSUD Dr. Soetomo Surabaya, East Java, Indonesia.

**Corresponding author:**
Birgitta Henny Perwitasari
birgittahenny@gmail.com

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## Abstract

**Introduction:** Congenital aniridia is a bilateral iris aplasia or hypoplasia associated with other ocular disorders. The purpose of this case report is to describe the clinical manifestation of congenital aniridia in two members of one family. **Case Presentation:** The first patient (mother) is a 43-year-old and the second patient (daughter) is a 12-year-old. Both patients complained of blurred vision since childhood. The visual acuity of the first patient was a positive light perception on the right eye (RE) and no light perception on the left eye (LE); the visual acuity of the second patient was 1/60 on the RE and 3/32 on the LE. Both patients had horizontal nystagmus and increased intraocular pressure (IOP) (N+1 palpation) in both eyes. Anterior segment abnormalities of both patients include aniridia with iris rudimentary and superiorly subluxated lens. The first patient also had LE corneal leukoma and RE cataract. The second patient also had right and left eye corneal conjunctivalization. Fundus examination showed no fundus reflex on the first patient and tigroid retina with foveal hypoplasia on the second patient. Eye ultrasounds of both patients showed vitreous opacity. **Conclusions:** Congenital aniridia primarily originates from a mutation in the paired box gene-6 (PAX6) and is associated with other ocular anomalies such as nystagmus, amblyopia, keratopathies, cataract, lens luxation, glaucoma, fovea, optic nerve hypoplasia. Patients in this case showed similar conditions between mother and daughter, however, the mother's condition was more advanced and more degenerated than the daughter's condition.

**Keywords:** congenital aniridia; lens subluxation; secondary glaucoma; familial aniridia

## Introduction

Congenital aniridia is a rare genetic eye disorder with total or partial absence of the iris from birth, and it is considered a rare disease, according to the National Organization for Rare Disorders[1] in the USA. The incidence of aniridia is between 1:64000 and 1:100000 births.[2] Congenital aniridia is typically due to autosomal dominant mutations in paired box gene-6 (PAX6) and approximately 2/3 of cases are familial, while 1/3 are sporadic.[3]

Patients with congenital anomalies are often diagnosed in early infancy because of the associated panocular anomalies such as iris hypoplasia, nystagmus, foveal hypoplasia, ptosis, and visual impairment. Due to the progressive nature of the ocular disease, the associated systemic abnormalities, and frequent complications, managing this condition requires a multidisciplinary approach involving pediatricians, ophthalmologists, and medical geneticists. The achievable goal for each patient is to maximize and maintain their visual capacity as much as possible.[4] Understanding the clinical manifestation of congenital aniridia is important for ophthalmologists to diagnose patients with congenital aniridia and give appropriate management and education.

## Case presentation

### The first patient

Patients in this case report consist of two patients who are related. The first patient was a 43-year-old woman who was the mother of the second patient. Both patients came to the outpatient clinic together at the same time with

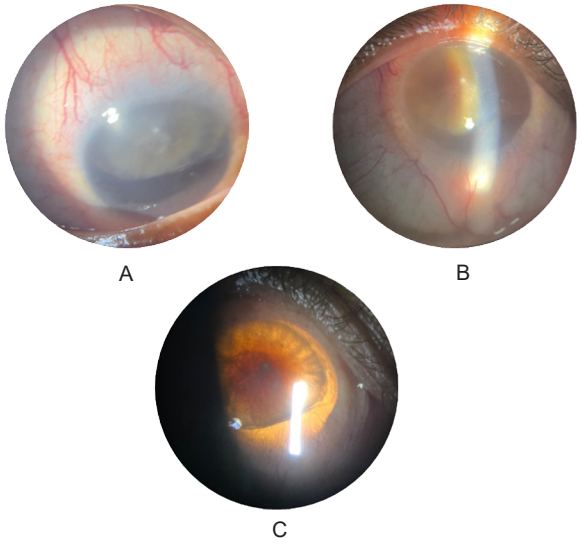


**Figure 1.** (A) The right eye's anterior segment of the first patient showed diffuse illumination; (B) Slit illumination; and (C) Retro illumination. Note: The condition of corneal conjunctivalization, aniridia, brunescent cataract lens, and superior lens subluxation.

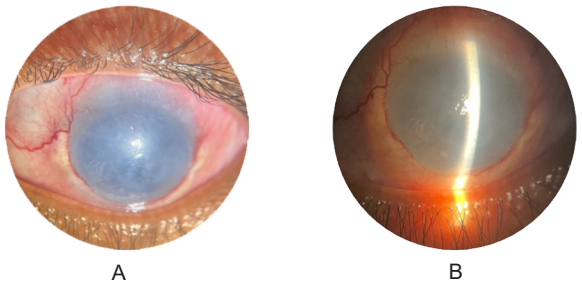


**Figure 2.** (A) The right eye's anterior segment of the first patient showed diffuse illumination; (B) Slit illumination; and (C) Retro illumination. Note: The condition of corneal conjunctivalization, aniridia, brunescent cataract lens, and superior lens subluxation.

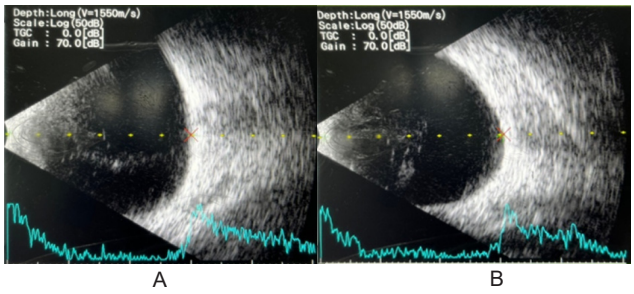


**Figure 3.** Eye ultrasound of the first patient's (A) right eye and (B) left eye.

chief complaints of blurred vision since childhood. They claimed they did not check their eyes sooner because of financial issues. After activating their national health insurance for medical treatment coverage, their eyes were checked by an ophthalmologist in their local town, and they were referred to our outpatient clinic.

The first patient stated that her vision gradually worsened in the last 13 years. Her left eye (LE) started to have a whitish appearance in the last 13 years. She often felt numb pain in both eyes accompanied by redness and watery eyes. She also complained of uncontrolled movement of both eyes since birth. She had no history of systemic diseases such as diabetes mellitus or hypertension.

Examination showed jerk horizontal nystagmus on both eyes of the first patient. Intraocular pressure (IOP) increased in both eyes, which was N+1 on palpation. The visual acuity was positive light perception on the right eye (RE) and no light perception on the LE. The anterior segment of the RE (Figure 1) showed corneal conjunctivalization and aniridia with rudimentary on inferior iris, cataract lens and superior lens subluxation.

The anterior segment of the first patient's LE (Figure 2) showed slight conjunctival hyperemia with corneal leukoma. The detailed examination of the anterior chamber, iris, and lens of the first patient's LE was difficult to evaluate because of corneal opacity.

Both eyes fundus examination of the first patient showed no fundus reflex, for which an ultrasound examination was performed. The ultrasound study of the first patient showed an axial length of 29.35 mm on the RE and 29.86 mm on the LE. A vitreous echogenic lesion on both eyes, shaped as particle and membrane approximately 30-40% RCS complex with mild mobility and retina on place (Figure 3).

The first patient was the second daughter of seven siblings. The patient's 5th younger brother and her father were known to have nystagmus, but both never got their eyes checked by an ophthalmologist. The first patient has two children; her first is a 20-year-old male with no eye abnormality, and her second is a 12-year-old female with similar eye complaints as the first patient. The patients' family tree can be seen in Figure 4.

To rule out WAGR (Wilms tumor, aniridia, genitourinary, mental retardation) syndrome, the first patient was referred to the urology department for a renal examination and ultrasound. The result of the renal ultrasound showed no abnormalities, and no Wilms tumor was found. The first patient also showed no signs of mental retardation and had no history of difficulties in following education at a normal school.

Phacoemulsification was done on the first patient's RE to remove the cataract and lens subluxation. However,

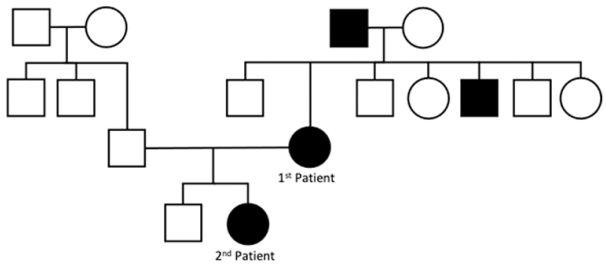


**Figure 4.** Family tree of the patients: Family members with similar eye abnormalities are shown in black shaded shapes (circles represent females and squares represent males).

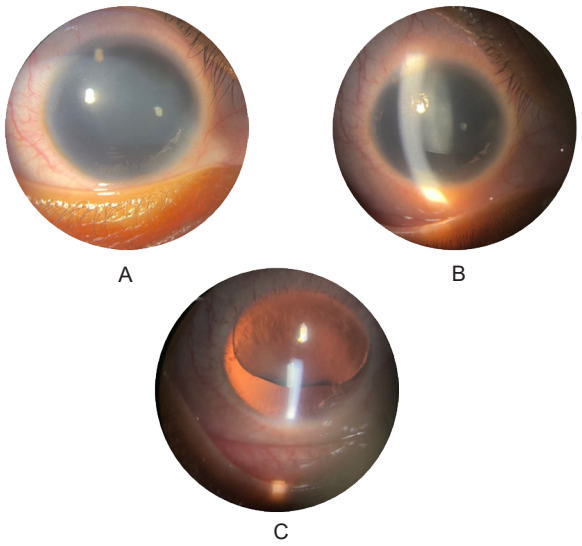

**Figure 5.** (A) The anterior segment of the right eye of the second patient showed diffuse illumination; (B) Slit illumination, and (C) Retro illumination. Note: The condition of corneal conjunctivalization, aniridia, and superior lens subluxation.

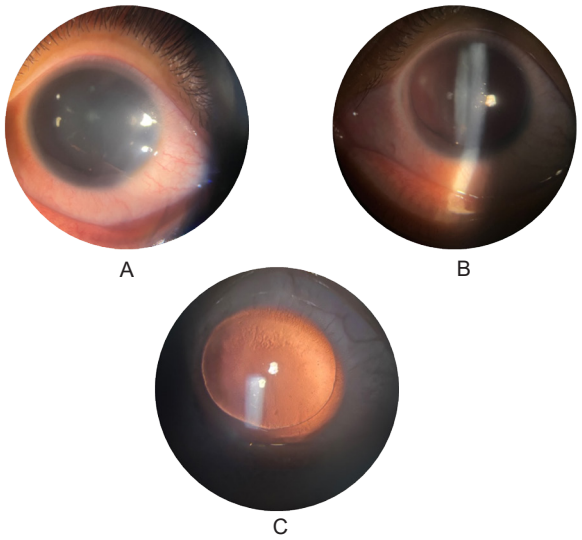

**Figure 6.** (A) The anterior segment of the left eye of the second patient showed diffuse illumination; (B) Slit illumination; and (C) Retro illumination. Note: The condition of corneal conjunctivalization and aniridia.

during the surgery, phacoemulsification was difficult because of the severity of lens subluxation; therefore, intracapsular cataract extraction (ICCE) was performed. Unfortunately, there was an intraoperative complication of suprachoroidal bleeding, and two months after surgery, the RE was starting to show signs of phthisis bulbi, so conservative treatment planning was given for the first patient.

## The second patient

The second patient is a 12-year-old female who experiences a similar ocular condition as her mother and also her uncle and grandfather from her mother's side (Figure 5). The second patient came with a chief complaint of blurred vision that gradually worsened in the last four years. Before that, the second patient claimed to be still

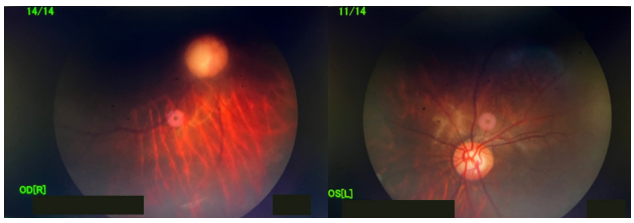

**Figure 7.** Fundus photography of (A) Right eye and (B) Left eye.

able to see well from both eyes. She also complained of uncontrolled movement of both eyes since birth. There were no complaints of eye redness, watery eyes, discharge, or pain. She had no history of systemic diseases such as diabetes mellitus, hypertension or allergies.

From the examination, there was jerk horizontal nystagmus on both eyes of the second patient. There was increased IOP in both eyes, which was 31.8 mmHg on both eyes. The best corrected visual acuity (BCVA) using the Snellen chart on the RE was $4/40^{-2}$ cc S-2.50 C-3.50 X90 → 4/25 with no pinhole improvement, and on the LE was $3/32^{-1}$ cc S-1.50 C-2.50 X90 → $4/25^{-1}$ with no pinhole improvement. The anterior segment of the RE (Figure 5) showed corneal conjunctivalization on the inferonasal cornea, aniridia, and superior lens subluxation. The anterior segment of the LE (Figure 6) showed corneal conjunctivalization on the inferior cornea and aniridia.

The fundus examination of the second patient in both eyes showed positive fundus reflex with the normal optic disc, but with tigroid retina and decreased foveal reflex in both eyes. However, a fundus photography examination cannot be done with satisfying results due to bilateral nystagmus (Figure 7).

The ultrasound study of the second patient showed an axial length of 29.31 mm on the RE and 29.00 mm on the LE. There was a vitreous echogenic lesion on both eyes, shaped as particle and membrane with approximately 20-30% RCS complex with mild mobility and retina on place (Figure 8).

The second patient was diagnosed with bilateral aniridia, RE lens subluxation and foveal hypoplasia in both eyes. The second patient was given IOP-lowering medications, which were timolol eyedrop twice daily for both eyes and latanoprost eyedrop once daily for both eyes. She also received spectacles with the education of near-visual aid devices and artificial tears.

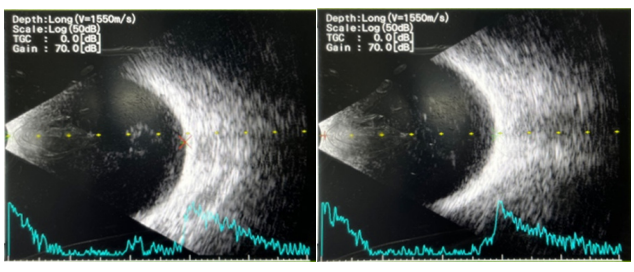

**Figure 8.** Eye ultrasound of the second patient's (A) RE and (B) LE.

To rule out WAGR syndrome, the second patient was referred to the urology department for a renal examination and ultrasound. The result of the renal ultrasound showed no abnormalities, and no Wilms tumor was found. The second patient also showed no signs of mental retardation and had no history of difficulties in following education at a normal school.

## Discussion and conclusions

Aniridia follows an autosomal dominant inheritance pattern. Approximately two-thirds of cases are familial, and one-third are sporadic. In roughly 90% of situations, aniridia is attributed to a mutation in the PAX6 gene found on the short arm of chromosome 11 (11p13). This gene encodes the PAX6 protein, a DNA-binding transcription factor.[5]

Congenital aniridia is frequently accompanied by other ocular anomalies such as nystagmus, amblyopia, keratopathies, cataract, lens luxation, glaucoma, fovea, and optic nerve hypoplasia. Aniridia often leads to secondary ocular problems, such as cataracts, aniridic keratopathy, and glaucoma.[5] Both patients in this case report had other ocular anomalies besides aniridia: nystagmus, keratopathy, lens luxation, and glaucoma.

Mutations in the PAX6 gene can give a diverse range of ocular manifestations, spanning from structural irregularities in the iris, nystagmus, underdevelopment of the fovea, cataracts, abnormalities in the cornea, optic nerve hypoplasia, glaucoma, to ptosis. Notably, a significant portion of individuals carrying PAX6 gene mutations also experience notable refractive errors affecting their vision.[6]

Ideally, genetic testing in a medical genetics laboratory is required for a definite diagnosis of aniridia syndrome. It is also helpful to clarify the status of other family members (parents and siblings) and the risk of having affected offspring.[4] However, genetic testing of both patients in this case was not done due to cost and equipment limitations.

Nystagmus, or repetitive, uncontrolled eye movements, usually appears between one and three months of age in aniridia caused by PAX6 mutations. This symptom is also the most common to lead to the diagnosis of aniridia because it is easily noticeable and causes patients to seek further medical treatment. Nystagmus in aniridia patients falls under the umbrella term of infantile nystagmus syndrome (INS) and is frequently associated with a vertical component.[7] In this case, both patients had bilateral horizontal nystagmus suspected to have occurred during early infancy. However, both patients did not immediately seek further medical treatment at the time of nystagmus occurrence due to financial issues.

Keratopathy affects 78–90% of patients with aniridia, and its prevalence and severity increase with age.

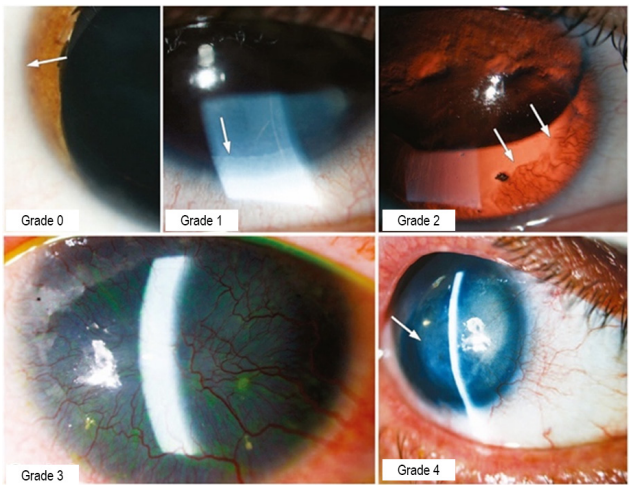


**Figure 9.** Grading scheme for aniridic-related keratopathy (AAK).[8]

Aniridic-related keratopathy (AAK) is characterized by peripheral vessels and superficial haze advancing from the conjunctiva towards the center of the cornea. A more severe condition of AAK is associated with the degradation or absence of the limbal palisades of Vogt. Limbal stem cell deficiency is likely involved in the pathogenesis of keratopathy in aniridia.[8]

AAK is graded based on its severity (Figure 9). In Grade 0, the limbal border is preserved without conjunctivalization into the cornea. In grade 1, a limbal pannus invades the cornea but remains within 1 mm from the limbus. In grade 2, the limbal pannus enters the peripheral and/or mid-peripheral cornea, but the central cornea is spared. The pannus can be observed better in retro illumination. In grade 3, the conjunctival tissue covers the central corneal region. In grade 4, the entire cornea is affected, with thickened, opaque lesion present. Corneal ulceration and scarring of the corneal stroma may develop and cause significant visual loss and eventual blindness.[8]

AAK can be managed through either supportive or surgical treatment. Supportive care involves the administration of artificial tear eyedrops. Surgical intervention for AAK includes options such as tarsorrhaphy, amniotic membrane transplantation, penetrating corneal transplantation, and limbal corneal transplantation. Given the limbal stem cell deficiency present in AAK, surgical treatments need to be able to provide a source of proliferating corneal epithelial cells.[8]

There is a recommended algorithm for the management of AAK according to its stages (Figure 10). Based on its severity, this algorithm divided AAK into five stages instead of four. Stage 1 and 2 are defined as abnormal peripheral epithelium. Stage 3 and 4 are central corneal epithelial changes with peripheral superficial neovascularization and superficial limbal stem cell deficiency. Stage 4 or 5 is defined as limbal stem cell deficiency with abnormal epithelium in the entire cornea, subepithelial fibrosis, deep and permanent stromal

scarring, and/or significant endothelial dysfunction. The treatment options for AAK on this algorithm are medical treatment, limbal stem cell transplantation and keratoprosthesis.[9]

In this case, the first patient showed grade 2 AAK in the right eye (Figure 1) and grade 4 in the left eye (Figure 2). The second patient showed grade 1 AAK in both eyes (Figures 5 and 6). These conditions were treated conservatively with artificial tears on both patients.

The prevalence of glaucoma in aniridia patients is approximately 70%. Early-onset glaucoma in aniridia patients is suspected to be caused by abnormalities of the Schlemm canal, whereas progressive changes in the iridocorneal angle cause later-onset glaucoma.[10] Eye drops that lower the intraocular pressure should be the first option in treating aniridic glaucoma before deciding the need for surgical interventions.[8]

Trabeculectomy may be considered in older children or adults with aniridic glaucoma. However, the long-term success of trabeculectomy in aniridia is relatively low because of an increased risk of developing fibrosis; therefore, the procedure should be augmented with antimetabolites.[8] In childhood glaucoma, surgery is the preferred treatment and angle surgery is the most frequently performed procedure.[11] If medical treatments are not successful in controlling IOP, implantation of a glaucoma drainage device can also be done for aniridia patients above infancy or early childhood.[8] In this case, the glaucoma condition of both patients was treated medically with eyedrops and oral IOP-lowering drugs.

In patients with aniridia, cataract happens in 95 of 247 (38.5%) phakic eyes and lens subluxation in 55 of 247 (22.3%) phakic eyes.[10] Cataract usually develops during the first two decades of life and typically evolves from a posterior polar opacity in the lens.[5] It has been suggested that cataract develops in a typical pattern in aniridia, where it evolves from posterior polar opacity to posterior subcapsular flecks or radial streaks that form a characteristic 'cartwheel' pattern.[8] The first patient, in this case, has a cataract, which is suspected to have developed around her late second decade of life, when she first started experiencing gradual blurred vision.

Lens extraction in aniridia presents unique challenges, including altered anterior chamber dynamics, abnormal capsule and zonule properties, and corneal opacification. Those factors, added with the decreased viability of the sulcus as an alternative location for an IOL, make lensectomy complicated.[8] However, Wang et al.[12] described the results after phacoemulsification and implantation of capsular tension ring and intraocular lens in ten aniridia patients with a mean age of 25.4 years, where visual acuity increased significantly after surgery.

Cataract extraction in aniridia patients is challenging; after cataract extraction, there is still aniridia to be solved. Implantation of prosthetic iris devices during cataract surgery has been described to eliminate

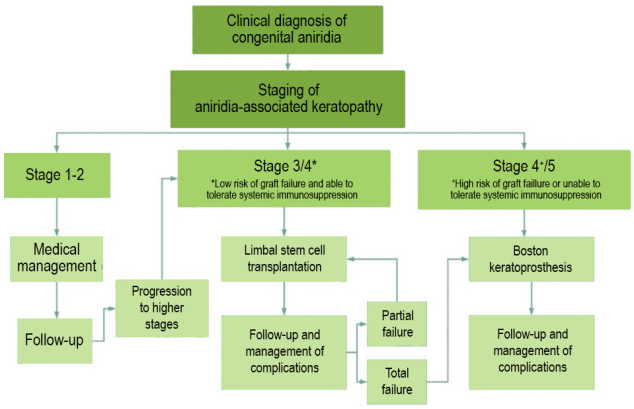


**Figure 10.** The recommended algorithm for managing aniridia-associated keratopathy according to the stage of corneal pathology.[9]

symptoms of photophobia induced by aniridia, although serious complications such as secondary glaucoma and corneal endothelial decompensation may occur after surgery.[12] One of the options for treating both cataracts and aniridia is using the black iris diaphragm IOL. The latest innovation is using an artificial iris implant, which is fully customized with handmade color composition, structurally matches the appearance of a natural iris and restores the aesthetic appearance.[13]

Lens dislocation was observed in 42% of patients with aniridia, and it is often displaced superiorly.[10],[14] The risk of lens dislocation may be caused by altered molecular structure in the zonules.[8] In this case, both patients have lens subluxation that displaced superiorly, but the first patient's lens also had cataracts. A lensectomy was done on the cataract eye of the first patient. Phacoemulsification was unsuccessful due to the severity of lens luxation, so ICCE had to be done. Unfortunately, there was an intraoperative complication of suprachoroidal bleeding which the intraoperative IOP changes could have caused.

Hypoplasia of the macular fovea is also a characteristic associated with aniridia. Abnormal structure of the fovea consistent with hypoplasia has been detected in 79–86% of subjects by fundoscopy.[6] The alterations included a lack of the typical light reflex and/or darker spot of the central macula and the presence of retinal vessels traversing the expected foveal area.[8] In this case, the fundus examination of the first patient could not be done due to dense cataract and corneal opacity, so the foveal hypoplasia condition could not be known in the first patient. For the second patient, there was a decreased foveal reflex in both eyes that could be caused by foveal hypoplasia.

For prompt congenital aniridia workup and follow-up, differentiation of isolated or syndromic aniridia is essential. Prompt diagnosis of WAGR or WAGR with obesity (WAGRO) is critical to avoid vital risks. An extensive ophthalmological workup must be performed to characterize the ocular phenotype, especially foveal hypoplasia, through spectral-domain optical coherence tomography (SD-OCT). Whenever possible, a genetic workup should be done to identify isolated deletions on

the PAX6 gene or deletions involving the Wilms' tumor 1 (WT1) gene. In sporadic cases and cases of WT1 deletion, a kidney ultrasound should be continued every three months until the age of seven. If no deletion is found, a molecular genetic test will be performed to confirm the clinical diagnosis and identify the pathogenic variants, allowing phenotype-genotype correlations.[15]

In overall condition, the two patients in this case showed similar conditions between a mother and her daughter but with more advanced and degenerated condition of the mother.

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