

# Insights from the 3<sup>rd</sup> Pan-European Conference on Congenital Aniridia and WAGR Syndrome

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<http://www.wagr.org>



*In Greek mythology, “Iris” was a goddess, the personification of the rainbow*

The purpose of this paper is to describe recent medical research and clinical consensus presented at the third Pan-European Conference on Congenital Aniridia and WAGR syndrome. It is hoped that this paper will be of assistance to patients, parents, and local clinicians, but it is not intended to provide medical advice.

**Topics:**

- **Ocular Surface Disease (OSD) and Aniridia-Associated Keratopathy (AAK)**
- **Genetics of Aniridia**
- **Artificial Iris**
- **Glaucoma**
- **Cataract**
- **Aniridia Syndrome**
- **Early Vision Development/Low Vision Care**
- **The Role of the BDNF gene**
- **Sleep Disturbances in Aniridia**
- **Aniridia in WAGR syndrome**
- **WAGR syndrome: clinical guidelines and Wilms tumor**

## Ocular Surface Disease (OSD)/Aniridia-Associated Keratopathy (AAK)

- Ocular Surface Disease (OSD)/AAK occurs at some point in more than 90% of patients with aniridia
  - Often begins in first decade of life
  - Often worsens after ocular surgery or treatment for glaucoma
  - Caused by limbal (stem cell) deficiency
  - **Extreme care should be taken to preserve the cornea in patients with congenital aniridia**
    - minimize number and extent of oculosurgical procedures whenever possible
    - minimize ptosis surgery (to decrease dry eye)
    - recognize ocular infections (“pinkeye”) promptly, treat with gentle antibiotics
    - use preservative-free, phosphate-free lubricants and eyedrops
    - avoid contact lenses unless therapeutic (scleral bandage lenses)
    - avoid VEGF antagonist eyedrops (bevacizumab, ranibizumab, pegaptamib)
- **Dry eye** may be first symptom of OSD in patients with aniridia
  - Is a risk factor for progressive Aniridia-Associated Keratopathy (AAK)
  - Measurement of amount of moisture on the cornea is an important tool for detecting and monitoring the degree of OSD in patients with aniridia
- **Nonsurgical treatment**
  - Goal of treatment is to avoid – or at least postpone – need for keratoplasty (cornea transplant)
  - Artificial tears
    - Should contain hyaluronic acid
    - semifluorinated alkanes (Novatears)
    - dexpanthenol ointment at night
  - Consider punctal occlusion (plug tear ducts), lid massage
  - Low-dose, unpreserved, phosphate-free steroid drops (Dexapos COMOD) or low-dose cyclosporine A (Ikervis)
  - Autologous serum drops
  - Amniotic membrane “patch”/Amniotic membrane extract eyedrops
  - Scleral bandage contact lens
- **Surgical treatment**
  - Only if significant reduction of visual acuity
  - Stem cell transplant
  - Cornea transplant (must include limbal cells)
  - **Boston Keratoprosthesis (“K-Pro”)** is an alternative to cornea transplant

- “Artificial cornea”
- May be indicated if patient unable to tolerate immunosuppressive drugs
- Indicated in Stage 4 AAK (light perception only)
- Increases risk of aniridia fibrosis syndrome
- Requires contact lens and antibiotic eye drops for life
- If glaucoma occurs before/after K-pro, can be controlled in about 80% of patients
  - If patient has a drainage tube, may need to be repositioned
  - If patient does not already have a drainage tube, may need one after K-pro
- K-Pro is risky, but appropriate if alternative is continued blindness
- Experimental/on the horizon: K-Pro with an internal intraocular pressure sensor

## Genetics of Aniridia

- To date, 952 different mutations of the PAX6 (aniridia) gene have been catalogued
- 90% of these involve premature truncation of a protein
- Genotype/phenotype correlation studies have begun to indicate:
  - Missense mutations are associated with a milder phenotype
  - Premature stop codons are associated with more severe phenotypes
  - WAGR syndrome (**deletion** of one copy of the PAX6 gene) may also be associated with more severe ocular phenotype

## Artificial Iris

- Multiple speakers urged caution, citing high complication rates, including induced glaucoma (52%) and worsening keratopathy (47%)
- One study compared the reasons parents and physicians give for considering artificial iris implants (decreased glare, improved appearance) and what patients with aniridia say about these concerns
  - The study found that patients’ priorities were not the same as parents/physicians:
    - patients reported substantially less difficulty with glare/photophobia than assumed
      - Degree of photophobia in 49 patients
        - None: 7
        - Moderate: 36
        - Significant: 2

- Severe: 4
  - patients felt strongly that improvements in cosmetic appearance did not warrant any risk to vision
- Artificial iris implants remain an experimental and controversial procedure

## Glaucoma

- Occurs in up to 75% of patients with aniridia
- May occur at any age (including at birth), but most commonly begins in childhood (average age at first occurrence: 8.5 yrs) or early adulthood. Risk increases with age
- Best way to measure intraocular pressure = applanation tonometry:
- Corneal thickness can affect measurement of pressure
  - Increased corneal thickness is common in aniridia
- Monitoring for glaucoma should be approximately every 6 months
  - If glaucoma develops, monitor more often
  - Glaucoma may develop after an initial exam with no evidence of glaucoma
- Poorer visual outcome if
  - Familial aniridia
  - Greater number of surgeries
- Treatment
  - **Medical**
    - eyedrops
  - **Surgical**
    - Trabeculotomy (preferred whenever possible)
    - Trabeculectomy
    - Drainage implants (Ahmed or Baerveldt)
      - Unpredictable/unstable hypotensive effect
      - Higher risk of complications (bleeding, scarring, choroid detachment)
    - Cyclodestructive procedures should be avoided
    - Laser procedures for the treatment of glaucoma in congenital aniridia are not useful and are associated with severe inflammatory response, lens subluxation, and acceleration of presenile cataracts
- Some patients do not respond to medical or surgical treatment

- Recent developments in surgical treatment of glaucoma:
  - “Minimally Invasive Glaucoma Surgery” (MIGS)
    - Early treatment is desirable
    - MIGS not as effective as traditional surgery but safer
    - Early (anecdotal) reports in aniridia are positive

## Cataract

- Incidence: 50-85% by age 20 years
- Reserve surgical intervention for cataracts until visual acuity is significantly impacted
  - Potential complications include: glaucoma, anterior fibrosis syndrome, ocular surface disease, retinal detachment
- Intraocular lens implant recommended, generally well-tolerated

## Aniridia Syndrome

“Aniridia syndrome” refers to increasing recognition among researchers and physicians that for many patients, the complications of PAX6 mutations/Aniridia involve multiple associated conditions in systems throughout the body.

- Aniridia syndrome may include:
  - Olfactory dysfunction (decreased or absent sense of smell)
  - Auditory processing deficits
  - Sensory processing deficits
  - Dental abnormalities
  - Sleep apnea
  - Sleep/Wake issues
  - Autism Spectrum Disorder
  - Cognitive/learning difficulties
  - Diabetes
  - Obesity
  - Polycystic Ovary Syndrome
  - Eczema
  - Abnormalities in the structure/function of the pancreas, including endocrine imbalances, chronic pancreatitis
- Statistics on 83 patients with familial or sporadic aniridia
  - Dental abnormalities 29 (35%)

○ Developmental delay	14 (17%)
○ Musculoskeletal abnormalities	11 (13%)
○ Asthma	10 (12%)
○ Depression	10 (12%)
○ Infertility	9 (11%)
○ Gallbladder disease	7 (8%)
○ Hypertension	6 (7%)
○ Diabetes	6 (7%)
○ Hyposmia (inability to smell)	4 (5%)
○ Pancreatitis	1 (1%)

## Early Development of Vision/Low Vision Care

- Vision in the first year of life:
  - Macular hypoplasia is common in aniridia
  - Both the retina and the macula continue to develop **after birth**
    - As a result, infants with congenital aniridia may appear to have very low vision in the first 6 months of life. Apparent visual acuity may improve dramatically by 9-12 months of age.
    - For this reason, infants and young children with congenital aniridia may benefit particularly from early interventions to stimulate development of vision
- Vision challenges throughout life:
  - photophobia/glare
  - decreased visual acuity
  - progressive visual impairment (increasing risk of ocular complications, decreasing visual acuity) is common as patients age
- Solutions:
  - Glare: sunglasses outdoors
    - Cold light sources indoors
  - Low Vision aids: magnifiers, telescopic spectacles, electronic reading devices
  - Orientation and Mobility: handheld telescopes, cane training
  - Early Intervention Services
  - Special Education
  - Vocational training and workplace equipment support

## Role of the BDNF gene

- Patients with BDNF haploinsufficiency (deletion of one copy of the BDNF gene) exhibit:
  - Hyperphagia (excessive hunger)
  - Childhood onset obesity
  - Intellectual disability
  - Impaired nociception (decreased response to pain)
- Therapies (possibly medications) which increase BDNF signaling could be helpful for treating obesity and neurodevelopmental disorders, both in patients with rare disorders and in the general population. Research is ongoing.

### **Sleep Disturbances in Aniridia**

- The PAX6 (aniridia) gene plays an important role in the development of the pineal gland (which produces the hormone melatonin). Patients with aniridia have:
  - Smaller pineal volume
  - Lower secretion of melatonin
  - Greater parental report of sleep disturbances in children
- Melatonin replacement therapy (supplements) may be helpful in both children and adults

### **Aniridia in WAGR Syndrome**

- Observation of 20 patients with WAGR syndrome, ages 2-39yrs:
  - 5 patients without intellectual disability (although 4 pts very young)
- Compared to patients with PAX6 mutation, patients with WAGR syndrome may have a more severe phenotype (ie, ocular complications at a higher rate and/or at a younger age)
  - Require oculosurgical intervention at a younger age
  - Require ophthalmologic exam under anesthesia more often/later in life due to inability to cooperate
  - Have a higher rate of/degree of:
    - Corneal complications
    - Glaucoma
    - Refractive errors
      - 3 patients with pathological myopia (extreme nearsightedness) and retinal detachment in one or both eyes



## WAGR syndrome: clinical guide and Wilms tumor

- WAGR is more than W-A-G-R
  - Absence of classic feature(s) does not exclude diagnosis. High level genetic testing required
  - Genital anomalies may be as frequent in females as in males, but are internal (ovaries, vagina, uterus) and may go undiagnosed
    - If abnormal ovaries, there is increased risk for gonadoblastoma/dysgerminoma (even in patients with XX karyotype)
- Hearing impairment: Auditory Processing Deficits (ASD) in >90%
  - Requires early identification and targeted interventions
- Impaired pain perception in 50%
  - Parents/physicians may need to rely on symptoms of injury/illness other than pain
- Autism Spectrum Disorder may be misdiagnosed
  - Behavioral symptoms may actually indicate some combination of Auditory Processing deficit, vision/cognitive impairment, Anxiety, and/or Attention Deficit Disorder/ADHD
  - Autism diagnosis may be helpful for obtaining wider range of educational services
  - Targeting therapies to actual deficits is most effective
- Late-onset renal failure affects 60% over age of 12
  - Lesion is focal segmental Glomerulosclerosis (FSGS)
  - Occurs in patients with WAGR who have not had Wilms tumor
  - Early diagnosis, aggressive treatment with ACE-inhibitor drugs slows progression
  - to end-stage renal failure (dialysis/transplant)
- Propofol (medication commonly used for general anesthesia) should be used with caution in WAGR patients with hypertriglyceridemia
  - Associated with acute pancreatitis
- Wilms tumor can occur in teens/adults with WAGR syndrome
  - Some level of surveillance is needed throughout life
  - No clear guidelines yet on type of imaging needed or appropriate frequency

- Treatment for Wilms tumor with Adriamycin is associated with late-onset congestive heart failure
  - Lifelong periodic cardiac evaluation is needed
- WAGR syndrome is extremely rare: more data is sorely needed
  - Patient registry is available to patients and physicians/researchers at <http://www.wagr.org>

### **How Can We Better Understand Aniridia and WAGR Syndrome?**

- Increased collaboration between researchers, and between researchers – patients – and patient advocacy organizations
- **“Databases are crucial”**

**Participate in the International WAGR Syndrome  
Patient Registry!**

[http://wagr.org/?page\\_id=3827](http://wagr.org/?page_id=3827)

**The 3<sup>rd</sup> Pan-European Conference on Congenital Aniridia and  
WAGR Syndrome**

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