WAGR syndrome: clinical features and guidelines for management

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Introduction

WAGR syndrome is a rare multiple congenital-anomaly syndrome caused by interstitial deletion of the distal portion of chromosome 11p13. Deletion size varies between individuals from 1 million to 26.5 million base pairs, with an average of 11 million base pairs. Variability in size of the genetic deletion is thought to account for the variable phenotype. WAGR is an acronym for the most prominent features: W is for Wilms tumor, A for aniridia, G for genitourinary anomalies, and R for range of developmental delays. Wilms tumor and genital anomalies are caused by deletion of the WT1 tumor-suppressor gene, and aniridia is caused by deletion of the PAX6 ocular development gene. Developmental delays are presumed to be the result of deletion of as yet unidentified genes in the region. Most cases are identified by chromosome studies of children with isolated aniridia and are due to de novo deletions, although a few familial translocations have been reported. Individuals with WAGR syndrome have a high risk for development of Wilms tumor and late-onset renal failure, as well as a variety of additional associated conditions.

Diagnosis

- Most cases of WAGR syndrome are identified in infants with isolated aniridia, 30% of whom will be positive for the characteristic deletion (11p13)
- In rare cases, aniridia may not be present. Children with Wilms tumor and genital anomalies may also warrant genetic testing
- Rare: balanced translocation in unaffected parent, Mosaic deletions
- Genetic testing
    - May begin with lymphocyte high-resolution chromosome study (at least 550 bands)
    - If the chromosomes are normal, then additional fluorescent in situ hybridization (FISH) studies should be done to identify deletion of the PAX6 gene (aniridia) and WT1 gene (Wilms tumor)
    - Array comparative genomic hybridization (aCGH) and multiplex ligation-dependent probe amplification (MLPA) may also be used to investigate deletion of clinically significant genes BDNF, EXT2, and ALX4

Clinical features and management

There is no cure for WAGR syndrome. However, children with WAGR syndrome benefit from early medical support and developmental interventions, including physical, occupational, and speech therapies. Special educational services are also beneficial. Life expectancy in WAGR syndrome has not been studied, but early detection and prompt treatment of life-limiting conditions such as Wilms tumor and end stage renal failure can improve the long-term prognosis.

Wilms Tumor

- Most common type of renal cancer in children
- Occurs in up to 50% of children with WAGR syndrome, most often between the ages of 1-3 years
- In rare cases may occur after age 8, and has been reported as late as age 19
- Surveillance should begin at birth/diagnosis of WAGR syndrome with abdominal ultrasound every 3 months until age 8. After age 8, ultrasounds may continue at less frequent intervals, along with periodic abdominal palpation and assessment for hypertension and hematuria
- Nephrogenic Rests/nephroblastomatosis are common in children with WAGR syndrome. Monitor closely for malignant transformation. In some cases, these lesions may require treatment with surgery and/or chemotherapy
- **Treatment**
    - Refer to Hematology/Oncology

Aniridia

- Iris hypoplasia
- Visual acuity is generally in the 20/100 to 20/200 range, but may be significantly decreased by any of the following
    - Microphthalmia
    - Hypoplasia of the optic nerve, macula, or fovea
    - Nystagmus
    - Amblyopia
    - Strabismus
    - Photophobia
    - Ptosis
    - Fragile cornea
        - Avoid use of contact lenses when possible
        - Use preservative-free eyedrops when possible
        - Treat conjunctivitis promptly
- Surgical intervention should be minimized to avoid complications
    - Aniridia fibrosis syndrome
    - Macular edema
    - Progression of aniridia-associated keratopathy
    - Glaucoma
- Artificial iris implant
    - Associated with increased incidence of glaucoma

- **Cataract**
    - Occurs in 50-85%
    - **Treatment**
        - Removal should be avoided unless vision is significantly obstructed
        - Surgery potentially more complex due to
            - Tunica vasculosa lentis
            - Capsular pseudoexfoliation
            - Lens subluxation or dislocation
            - Fragile anterior capsule

Aniridia (cont.)

- **Glaucoma**
  - Occurs in 50% by age 8. Risk increases with age
  - Increased corneal thickness is common
  - Exam under anesthesia may be necessary in young children
  - **Treatment**
    - Use preservative-free medication when possible
    - Surgical interventions include
      - Goniotomy (may be considered in young infants with aniridia and glaucoma)
      - Trabeculotomy, trabeculectomy, and trabeculectomy with mitomycin C
      - Glaucoma drainage devices (Baerveldt, Ahmed, or Molteno tube shunts)
      - Laser and cyclodestructive procedures are not useful in aniridia. These procedures are associated with severe inflammatory response, lens subluxation, and acceleration of presenile cataracts

- **Aniridic-associated Keratopathy**
  - Progressive opacification of the cornea
  - Occurs in more than 90%
  - Multiple causes including limbal cell deficiency, abnormal tear film
  - Exacerbated by injury to the cornea: infection, irritation, surgery
  - Often begins in the first decade of life, but may not affect vision until adulthood
  - **Treatment**
    - Preservative-free, phosphate-free lubricant drops
      - Hyaluronic acid, semifluorinated alkanes, dexpanthenol ointment at night
    - Warm compresses and lid massage
    - Punctal plugs
    - Low-dose Cyclosporine A eye drops
    - Autologous serum or plasma eye drops
    - Amniotic membrane extract eye drops or patch
    - Avoid use of VEGF antagonist eye drops
    - Cornea/limbal stem cell transplant
    - Boston Keratoprosthesis (K-Pro)

Genitourinary Anomalies

- Males
  - Cryptorchidism
  - Hypospadias
  - Micropenis
  - Hypoplastic scrotum
- Females
  - Streak ovaries
    - Occur in XX females with WAGR syndrome
    - Rare cases of gonadoblastoma reported
    - Monitor with pelvic ultrasound or MRI and/or laboratory tests
  - Malformations of the uterus, fallopian tubes, vagina
- Ambiguous genitalia
- Duplicated or ectopic ureter
- Hypoplastic or horseshoe kidney
- Unilateral renal agenesis
- Renal cysts
- **Treatment**
  - Refer to Urology, Gynecology

Range of Developmental Delay

- May be mild to severe. Mild to moderate intellectual disability is most common (IQ 50 to 70)
- Some individuals with normal/near-normal IQ
- **Treatment**
  - Refer to Early Intervention Services

Auditory and Sensory Processing Disorders

- Auditory Processing Disorder occurs in more than 90%
  - **Treatment**
    - Refer to Audiology, Speech therapy
- Sensory Processing Disorder mild to severe
  - **Treatment**
    - Refer to Occupational therapy

BDNF Gene Deletion

- Haploinsufficiency of Brain-Derived Neurotrophic Factor
- Occurs in 50%
- Associated with
  - Obesity
  - Hyperphagia
    - May involve severe food-seeking behaviors
    - May require strict control of access to food
- Associated with (cont.)
  - Decreased behavioral response to pain
    - May not display discomfort even with significant illness or injury
    - May require careful observation for signs of illness or injury
  - Decreased cognition
- **Treatment**
  - Refer to Dietician

Behavioral and Psychiatric Disorders

- Anxiety Disorder
- Attention-Deficit Hyperactivity Disorder (ADHD)
- Autism
  - A few individuals meet criteria for diagnosis of Autism
  - Autistic-like behaviors are more common and may reflect a combination of intellectual disability, vision impairment, Auditory/Sensory Processing Disorder, and/or Anxiety Disorder
  - Accurate diagnosis is important to effective treatment
- Depression
- Obsessive-Compulsive Disorder
- Tantrums, “Meltdowns,” Aggression
- **Treatment**
  - Refer to Neuropsychiatry if available. Team approach to diagnosis may be most effective

Chronic Kidney Disease

- Focal Segmental Glomerulosclerosis (FSGS)
- Occurs in 60%
- Symptoms
  - Hypertension
  - Proteinuria
  - Hypertriglyceridemia
- **Treatment**
  - Refer to Nephrology
  - Early diagnosis and aggressive treatment with ACE-inhibitor medication may slow progression, sometimes for many years
  - Dialysis or renal transplant

Cardiopulmonary Abnormalities

- Congenital defects
  - Patent foramen ovale
  - Atrial or Ventricular septal defects
  - Valvular hypoplasia
  - Patent ductus arteriosus
  - Pulmonary hypertension
  - Tetralogy of Fallot
- Cardiomyopathy
  - May occur in patients treated with doxorubicin for Wilms tumor
  - Requires lifelong surveillance
- Tracheomalacia, laryngomalacia, bronchomalacia
- Recurrent pneumonia
- Obstructive sleep apnea
- **Treatment**
  - Refer to Cardiology
  - Refer to Pulmonology/Sleep specialist

Head, Ears, Nose, Throat

- Enlarged parietal foramina
- Low-set ears, pinna abnormalities
- Enlarged tonsils and/or adenoids
  - Tonsillectomy/adenoidectomy common
- Recurrent otitis media
  - Tympanostomy tube placement common
- Recurrent sinusitis
- High-arched palate, cleft palate
- Narrowing of the pharynx
- Micrognathia
- Small, missing, misshapen teeth, dental malocclusion, delayed loss of primary teeth
- Hearing impairment (sensorineural)
- Abnormal brainstem response or abnormal Auditory Evoked Potential
  - Occurs in 50%
- **Treatment**
  - Refer to Audiology, ENT, Dentist

Gastrointestinal Abnormalities

- Acute or chronic pancreatitis
  - Risk increased if hypertriglyceridemia present
  - Propofol may increase risk of acute pancreatitis
- Gastroesophageal Reflux Disease (GERD)
- Chronic constipation
- Feeding issues
- Gallstones, cholesterolosis
- Biliary atresia
- Intestinal malrotation
- Diaphragmatic hernia
- **Treatment**
  - Refer to Gastroenterology

Metabolic and Endocrine Abnormalities

- Early onset obesity
  - Investigate for BDNF gene deletion
- Insulin resistance
- Diabetes
- Dyslipidemia
- Precocious puberty
- **Treatment**
  - Refer to Endocrinology

Musculoskeletal Abnormalities

- Hypertonia/hypotonia
- Toe-walking
- Metatarsal adductus
- Talipes
- Syndactyly, Clinodactyly
- Hemihyperplasia
- Short stature
- Scoliosis
- Osteochondromatosis
- **Treatment**
  - Refer to Orthopedics

Neurologic Abnormalities

- Microcephaly
- Hypoplastic pineal gland
  - Melatonin supplementation may be useful for sleep disorders
- Absent or hypoplastic cranial nerves
  - Olfactory
  - Abducens
- Agenesis of the corpus callosum
- Intracranial Hypertension
- Epilepsy
- **Treatment**
  - Refer to Neurology

Sleep Disorders

- Hypoplastic pineal gland
- Obstructive sleep apnea
- **Treatment**
  - Melatonin supplementation
  - Continuous positive airway pressure (CPAP)