Glaucoma Associated With Axenfeld-Rieger Spectrum and Peters Sequence

Developmental anomalies of the anterior segment can result in glaucoma that is difficult to control and may have genetic implications for the patient’s family as well as associated systemic abnormalities.

BY ANURADHA GANESH, MD, AND ALEX V. LEVIN, MD, MHS, FRCSC

The childhood glaucomas are a heterogeneous group of disorders that can cause serious and permanent visual damage. The term developmental glaucoma broadly encompasses all glaucomas resulting from abnormal development of the aqueous outflow system. The developmental glaucomas are termed primary or secondary, depending on whether the abnormality of the aqueous outflow pathway exists in isolation (trabeculodysgenesis) or in association with another anterior segment developmental anomaly (ASDA).

The anterior segment’s development involves the surface ectoderm (lens and corneal epithelium), neuroectoderm (posterior epithelium of the iris and ciliary body, sphincter and dilator muscle of the iris), and neural crest (corneal stroma and endothelium, iris and ciliary body stroma, trabecular meshwork, and Schlemm canal). This complex process is controlled by a molecular genetic network involving multiple signals, their receptors, and transcription factors. Mutations in these developmental genes lead to ASDA and contribute to the pathogenesis of pediatric glaucoma.

The ASDAs are characterized by marked phenotypic and genetic heterogeneity and by variability in expression. They include distinct ocular entities as well as overlapping phenotypes. ASDAs are often associated with glaucoma due to associated goniodysgenesis. This article focuses on two of the more common ASDAs.

AXENFELD-RIEGER SPECTRUM
Characteristics and Genetics

The Axenfeld-Rieger spectrum (ARS) is characterized by an anteriorly displaced, prominent Schwalbe line (posterior embryotoxon), usually with attached iris strands in combination with varying degrees of iris malformation such as iris hypoplasia, polycoria, corectopia, and ectropion uveae (Figure 1). Approximately 50% of patients with ARS develop secondary glaucoma due to impaired, abnormal aqueous outflow secondary to the incomplete development of the trabecular meshwork and Schlemm canal. Glaucoma may present at birth or may not occur until adulthood.

Characteristic nonocular features may or may not be present. They include mild dysmorphism (hypertelorism, broad flat nose, maxillary hypoplasia, and mild prognathism), dental anomalies (microdontia, hypodontia, anodontia, oligodontia, or cone-shaped teeth), redun-
dant periumbilical skin, cardiac outflow tract malformations, pituitary abnormalities, growth retardation, and hypospadias. The ocular involvement in ARS is usually bilateral, but it may be asymmetric and, rarely, unilateral.

ARS is an autosomal dominant condition. Three genetic loci associated with ARS are RIEG1 at 4q25 (PITX2), RIEG2 at 13q14 (gene not identified), and RIEG3 at 6p25 (FOXC1). It has also been described in association with mutations in GJA1 and COL4A1, the latter in association with brain malformations. Multiple syndromes have also been described such as SHORT (short stature, hyperextensibility/hernia, ocular depression [ie, enophthalmos], Rieger anomaly, and teething abnormalities).

**Treatment**

Therapy of a patient with ARS should involve surveillance for both ocular and systemic abnormalities. Pupilloplasty is rarely required. Despite sometimes severe malformation, vision can be remarkably good. Glaucoma is initially managed with medications, with aqueous suppressants generally being more effective than miotics. Goniotomy or trabeculotomy may be difficult to perform due to iris adhesions, and in the authors’ experience, tissues are stiff and resistant to this surgical intervention. Surgeons should therefore consider primary trabeculotomy or tube implantation when medication fails.

When the diagnosis of ARS is made, parents and other family members must be examined. The presence of anomalous anterior segment features may facilitate an early diagnosis of ARS and the establishment of appropriate lifelong screening for glaucoma. Molecular genetic testing is also available. The disorder can be heritable regardless of the presence or absence of systemic features.

**PETERS SEQUENCE**

**Characteristics and Genetics**

Peters anomaly is a rare congenital ASDA. It is a malformation sequence in which incomplete “pinching off” of surface ectoderm to form the embryonic lens prevents normal neural crest migration. This ASDA is characterized by a central or eccentric, localized, posterior corneal defect with overlying corneal opacification with or without iridocorneal or lenticular-corneal adhesions (Figure 2). The peripheral cornea is usually clear but may be scleralized. There may be vessels growing into the corneal opacity. Eighty percent of cases are bilateral.

Glaucoma may occur in 50% to 70% of patients with Peters anomaly. As with ARS, glaucoma occurs due to an incomplete development of the trabecular meshwork and Schlemm canal. The glaucoma may present at birth, or it may develop in childhood or even later.

Peters anomaly may be seen in association with Axenfeld-Rieger syndrome and aniridia. The globe is microphthalmic in 50% of patients. Approximately 60% of patients—usually when the disorder is bilateral—present with systemic anomalies that may include craniofacial anomalies, congenital heart disease, pulmonary hypoplasia, syndactyly, ear anomalies, genitourinary disorders, and central nervous system anomalies. Peters anomaly has been reported with fetal alcohol syndrome.

The Peters-plus syndrome is a specific malformation complex due to involvement of the B3GALT1 gene, which is characterized specifically by short stature (skeletal dysplasia) as well as other malformations.

Although most cases are sporadic, autosomal recessive and dominant inheritance have been reported. Mutations in the PAX6, PITX2, FOXC1, and CYP1B1 genes have each been associated with Peters sequence.

**Treatment**

Definitive management of congenital corneal opacification in Peters anomaly usually involves penetrating keratoplasty (PKP), although in some cases, especially if PKP is not available, optical iridectomy or autorotation keratoplasty have been used. PKP has been recommended for patients ranging in age from 2 to 12 months old. Zaidman and coworkers reported a graft success rate of 83% in patients with Peters anomaly, but additional procedures and repeat PKP may be needed. The lens is often lost at PKP surgery, leaving the patient aphakic and at risk of aphakic glaucoma. Glaucoma adversely affects the prognosis of PKP in Peters anomaly. Frequent follow-up, high-dose topical steroid therapy, early suture removal (within 4-6 weeks), and aggressive and early ambylopia therapy are mandatory for optimal postoperative outcomes.

Glaucoma in Peters sequence can be extremely dif-
difficult to control and typically requires surgical intervention. Trabeculotomy is frequently ill advised due to the shallow peripheral anterior chamber that is often present. Goniotomy becomes technically challenging, even when assisted by ocular endoscopy. Tube implantation can be difficult due to the anterior chamber anatomy. Trabeculectomy with adjunctive mitomycin C may be necessary. In aphakic patients, endoscopic cyclophotocoagulation becomes a viable option.

Glaucoma surgery, with medical therapy, may provide long-term IOP control in one-third of eyes. Despite successful IOP control, visual results are often poor due to uncontrolled glaucoma and amblyopia. Postoperative complications such as graft failure, cataract, inoperable retinal detachment, and phthisis are not uncommon and will further adversely affect outcomes.

This work was supported in part by the Foerderer Foundation.

Anuradha Ganesh, MD, is a consultant, pediatric ophthalmology, in the Department of Ophthalmology at Sultan Qaboos University Hospital in Muscat, Oman.

Alex V. Levin, MD, MHSc, FRCS, is the chief of pediatric ophthalmology and ocular genetics at Wills Eye Institute, Thomas Jefferson University, Philadelphia. Dr. Levin may be reached at (215) 928-3914; alevin@willseye.org.