Familial Axenfeld-Rieger Anomaly, Atrial Septal Defect, and Sensorineural Hearing Loss

A Possible New Genetic Syndrome

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Objective: To describe the clinical and ocular histopathological findings in multiple members of a family with congenital Axenfeld-Rieger anomaly, atrial septal defect, and sensorineural hearing loss.

Methods: We performed a retrospective review of the medical charts and the ocular histopathological material of multiple members of a family.

Results: Congenital Axenfeld-Rieger anomaly and glaucoma were inherited by both the proband and her male half-sibling from a phenotypically positive father and 2 different phenotypically negative mothers, suggesting an autosomal dominant inheritance. The proband’s male half-sibling and her father also had atrial septal defects and sensorineural hearing loss. The proband’s paternal grandmother had severe glaucoma. Histopathological analysis of blind, painful eyes removed from the proband’s father and paternal grandmother showed incomplete development of the anterior chamber angle with iris stromal hypoplasia, prominent posterior embryotoxon with iris adhesions, and abnormal position and insertion of the ciliary muscles.

Conclusions: This is the first description of coexisting Axenfeld-Rieger anomaly, atrial septal defect, and sensorineural hearing loss in multiple members of a single family. The iris, trabecular meshwork, and large portions of the cardiac intraventricular septum all arise from neural crest anlagen, thus supporting the notion that anterior segment dysgenesis represents a developmental disorder of the neural crest.


AXENFELD-RIEGER anomaly (ARA) is an autosomal dominant–inherited ocular disorder characterized by iris stromal hypoplasia, angle abnormalities, and a prominent and an anteriorly displaced Schwalbe line (posterior embryotoxon), often with adherent iris strands.1-3 Somatic defects may accompany ARA, including maxillary hypoplasia, hypodontia, umbilical hernia, and hypospadias. This combination of ocular and somatic anomalies is termed “Axenfeld-Rieger syndrome” (ARS).1-3 Iridogoniodygenesis anomaly shares with ARA autosomal dominant inheritance, iris stromal hypoplasia, and angle abnormalities but lacks posterior embryotoxon.4-7 Iridogoniodygenesis, like ARA, may be accompanied by maxillary hypoplasia, hypodontia, umbilical hernia, and hypospadias, in which case it is termed “iridogoniodygenesis syndrome.”7-11 Autosomal dominant iris hypoplasia without angle abnormalities, posterior embryotoxon, or somatic anomalies has also been described.12 Glaucoma occurs frequently in patients with each of these conditions.1-12

The clinical similarity between the anterior segment dysgenesis syndromes led Shields and coworkers2,3 to suggest that these anomalies form an overlapping spectrum of disorders. This notion has gained support from recent genetic linkage studies of families with ARS,13,14 iridogoniodygenesis syndrome,7 and autosomal dominant iris hypoplasia,12 each of which mapped the genetic locus in the affected families to the long arm of chromosome 4, specifically, 4q25. However, families with ARA,15 ARS,16 and iridogoniodygenesis anomaly7,17 have been mapped to loci other than 4q25 as well, emphasizing the genetic heterogeneity of this group of disorders.

Detailed studies of the embryologic origin of anterior segment structures and of the craniofacial skeleton in birds18,19 and rodents20 have led to the theory that the anterior segment dysgenesis syndrome represents a neurocristopathy, or primary developmental disorder of the neural crest.2,5,21-24 This view has been sup-
SUBJECTS AND METHODS

The proband, her father, and her half-brother each received eye care at the Wilmer Ophthalmological Institute, Baltimore, Md. In addition, each had an abdominal ultrasound to exclude possible renal masses or dysgenesis, the proband had a 2-dimensional echocardiogram with Doppler to rule out cardiac abnormalities, and the proband’s stepmother (case III-6, Figure 1) received complete ophthalmic and cardiac examinations. The general ophthalmic and cardiac status of the remaining members of the family was obtained by history from the proband’s father and stepmother (cases III-5 and III-6, respectively, Figure 1).

The proband (case IV-3, Figure 1), now 30 years of age, was first seen by the ophthalmology service at 6 months of age with increased intraocular pressures. The proband’s male half-sibling (case IV-4, Figure 1), now 22 years of age, first approached the ophthalmology service at 10 months of age with evidence of glaucoma. At 2 years of age he was referred to the cardiology service for evaluation of a murmur and failure to thrive, at which time he was found to have an atrial septal defect requiring surgical repair. The proband’s father (case III-5, Figure 1), now 50 years of age, first approached the ophthalmology service in early infancy with increased intraocular pressures. Failure of both medical and surgical therapies resulted in enucleation of a blind, painful left eye at 10 years of age. Independently, the proband’s father was found to have an atrial septal defect at 11 months of age, which eventually required surgical repair. The proband’s paternal grandmother (case II-6, Figure 1), now deceased, was first seen at 38 years of age with end-stage glaucoma and central retinal vein occlusion of the left eye that required enucleation.

CASE IV-4

The proband’s male half-sibling (case IV-4, Figure 1) was the product of a full-term, uncomplicated pregnancy of nonconsanguineous parents. He was well until 10 months of age, at which time he was found to have elevated intraocular pressures that have since been controlled with combined medical and surgical therapy. Current ocular medications include 0.5% timolol maleate and 0.1% dipivefrin hydrochloride, 1 drop each to the left eye twice a day. Recent ophthalmic examination findings showed a best-corrected visual acuity of 20/40+2 OD and 20/25 OS. Pupils were 2 mm, reactive to 1 mm, with no relative afferent defect. Extraocular motility was full, with an intermittent esotropia of 30 prism diopters at a distance and near. Hertel measurements were 16 mm on the right and 19 mm on the left with a base of 94 mm. Visual fields were full to counting fingers in both eyes. External examination results were normal. Intraocular pressures were 15 mm Hg on the right and 20 mm Hg on the left. Slitlamp examination of the right eye showed a conjunctival bleb at the 8:30–o’clock position. The cornea was clear but with prominent temporal and nasal anterior embryotoxon. The iris had several surgical peripheral iridectomies and stromal hypoplasia (Figure 2). On slitlamp examination of the left eye the conjunctiva was unremarkable. The left cornea had Haab striae and prominent temporal and nasal anterior embryotoxon. The iris had a large surgical peripheral iridectomy at the 10–o’clock position, stromal hypoplasia, and several posterior synechiae. Gonioscopy showed rare peripheral anterior synchiae and diffuse, circumferentially oriented dilated iris blood vessels in each eye. Indirect ophthalmoscopy revealed a cup-disc ratio of 0.3 bilaterally and was otherwise normal.

Physical examination findings were notable for grossly normal hearing, normal craniofacial and dental development, no palpable intra-abdominal masses or umbilical hernia, and normal cardiac findings. A 2-dimensional echocardiogram with Doppler disclosed no evidence of ventricular, valvular, or septal defects. Renal ultrasonography showed separate kidneys of normal size and shape, without masses or hydronephrosis.

RESULTS

THE PROBAND: CASE IV-3

The proband (case IV-3, Figure 1) was the product of a full-term, uncomplicated pregnancy of nonconsanguineous parents. She was well until 6 months of age, at which time she developed a traumatic subdural hematoma that required surgical evacuation. She currently has no permanent neurologic deficits, although a recent computed tomographic scan of the head demonstrated moderate residual ventriculomegaly.

A full ophthalmic evaluation performed at 6 months of age revealed elevated intraocular pressures, which have since been controlled with combined medical and surgical therapy. Current ocular medications include 0.5% timolol maleate and 0.1% dipivefrin hydrochloride, 1 drop each to the left eye twice a day. Recent ophthalmic examination findings showed a best-corrected visual acuity of 20/40+2 OD and 20/25 OS. Pupils were 2 mm, reactive to 1 mm, with no relative afferent defect. Extraocular motility was full, with an intermittent esotropia of 30 prism diopters at a distance and near. Visual fields were full to confrontation. External examination results were normal. Intraocular pressures were 20 mm Hg on the right and 21 mm Hg on the left. Slitlamp examination on the right showed a clear cornea with no posterior embryotoxon. The iris had stromal hypoplasia and several areas of increased translucency. Slit-
lamp examination of the left eye revealed temporal posterior embryotoxon, iris stromal hypoplasia, and areas of increased translucency. The lens and vitreous were clear bilaterally. Gonioscopy showed iris strands to Schwalbe line in each eye. Indirect ophthalmoscopy revealed a cup-disc ratio of 0.3 bilaterally and was otherwise normal.

The proband’s male half-sibling was referred to the cardiology service for evaluation of a murmur and failure to thrive at 2 years of age. Two-dimensional echocardiography with Doppler revealed an ostium secundum atrial septal defect measuring approximately 2×4 cm, with otherwise normal cardiac anatomy. Surgical correction was performed without complications.

Physical examination results were notable for moderate sensorineural hearing loss bilaterally. Otherwise, craniofacial and dental development was normal, no palpable intra-abdominal masses or umbilical hernia were present, and there was no evidence of hypospadias. Renal ultrasonography showed separate kidneys of normal size and shape, without masses or hydronephrosis.

CASE III-5

The proband’s father (case III-5, Figure 1) was the product of a full-term, uncomplicated pregnancy of nonconsanguineous parents. He was well until early infancy, at which time he was found to have elevated intraocular pressures. Failure of both medical and surgical therapies resulted in enucleation of a blind, painful left eye at 10 years of age. Intraocular pressure in the right eye has been controlled with combined medical and surgical therapy. Current ocular medications include 0.5% timolol maleate and 2% epinephrine hydrochloride, 1 drop each to the right eye twice a day, and acetazolamide sodium, 250 mg 3 times a day. Recent ophthalmic examination findings showed a best-corrected visual acuity of 20/100 OD. The pupil was irregular. Extraocular motility was full. The visual field was markedly constricted. Intraocular pressure was 12 mm Hg. Slitlamp examination showed mild band-shaped keratopathy, Haab striae, temporal and nasal posterior embryotoxon, and large peripheral iridectomies at the 11-o’clock position and from the 7- to the 10-o’clock position. Gonioscopy showed scattered peripheral anterior synchiae and multiple iris strands to a prominent Schwalbe line. Indirect ophthalmoscopy showed end-stage cupping with little neural rim remaining.

Microscopic examination of the enucleated left eye disclosed incomplete development of the anterior chamber angle, with most of the longitudinal muscle bypassing a hypoplastic scleral spur and inserting directly into the trabecular meshwork (Figure 3). The circular portion of the ciliary muscle was displaced anteriorly (Figure 3, A). The angle was incompletely cleaved. Prominent temporal and nasal posterior embryotoxon with iris adherent were present. Healed tears in the Descemet membrane (Haab striae) and iris stromal hypoplasia were also observed.

At 11 months of age the patient was referred to the cardiology service for evaluation of a cardiac murmur. Cardiac fluoroscopy revealed bilateral ventriculomegaly and an enlarged left atrium. Surgery was performed when the patient was 9 years old, at which time a 6×3-cm atrial septal defect of the secundum type was repaired. No other cardiac anomalies were noted.

Physical examination results revealed marked bilateral sensorineural hearing loss but normal craniofacial and dental development, no palpable intra-abdominal masses or umbilical hernia, and no evidence of hypospadias. Renal ultrasonography showed separate kidneys of normal size and shape, without masses or hydronephrosis.

CASE II-6

The proband’s paternal grandmother (case II-6, Figure 1) was the product of a full-term, uncomplicated pregnancy of nonconsanguineous parents. She received no ophthalmic attention until 38 years of age, when she had end-stage glaucoma and a central retinal vein occlusion in her left eye, which was enucleated. Microscopic examination of the left eye disclosed incomplete development of the anterior chamber angle, with most of the ciliary body inserting directly into the trabecular meshwork.
forward location of the circular portion of the ciliary body; prominent temporal and nasal posterior embryotoxon with adherent iris (Figure 4, A and B); and iris stromal hypoplasia (Figure 4, C). Details of further ophthalmic and cardiac examinations were not available. She was reported by her son, the proband’s father (case III-5), to have had no known heart murmur, exercise intolerance, renal disease, or hearing loss. She died after a myocardial infarction at 65 years of age.

OTHER RELATIVES

The proband’s stepmother (case III-6, Figure 1) had complete ophthalmic and cardiac examinations, both of which showed normal results. The proband’s biological mother (case III-4, Figure 1) and the remaining members of the family were not available for examination but were reported by the proband’s father to have had no known heart murmur, exercise intolerance, renal disease, or hearing loss. She died after a myocardial infarction at 65 years of age.

COMMENTS

We describe 3 generations of a family with congenital ARA and glaucoma. The passage of ARA to male and female half-siblings by a single phenotypically positive father and 2 different phenotypically negative mothers provides strong support for an autosomal dominant mode of inheritance, as has been suggested in previous studies of families with the anterior segment dysgenesis syndromes. Although the anterior segment defects observed in the 4 affected family members (cases II-6, III-5, IV-3, and IV-4) were severe, resulting in early onset of glaucoma, many analyses have described a more variable expressivity, a feature characteristic of most autosomal dominant disorders.

Only 2 male family members (cases III-5 and IV-4) had documented atrial septal defect and sensorineural hearing loss, perhaps suggesting that the transmission of the traits observed in multiple family members was coincidental and not directly linked. However, as with the anterior segment dysgenesis syndromes, most families with syndromic atrial septal defect or sensorineural hearing loss have reported an autosomal dominant transmission with variable expressivity. Moreover, individual cases of ARS associated with sensorineural hearing loss or cardiac malformation have been reported, including a single case with a ventricular septal defect. Of note, early deletion studies described both sensorineural hearing loss and cardiac anomalies, including atrial septal defects, in children with large segmental and terminal deletions of 4q, an important finding given the recent report by Walter et al that most syndromic forms of anterior segment dysgenesis are directly linked to 4q25. We believe, therefore, that the ARA, atrial septal defect, and sensorineural hearing loss in this family were closely linked and cotransmitted in an autosomal dominant manner, and that the apparent independence of their segregation was attributable entirely to variable expressivity.

The genetic cotransmission of ARA, atrial septal defect, and sensorineural hearing loss in this family supports the notion that the anterior dysgenesis syndromes...
represent a primary neurocristopathy. The mesodermal derivatives of the anterior segment of the eye, as well as large portions of the cardiac intraventricular septum, have been shown to arise from neural crest anlagen. In addition, sensory neurons of the vestibuulocoustic ganglia, which are themselves derived from cephalic ectoderm, seem to rely heavily on underlying neural crest derivatives for appropriate development. Similarly, indirect mechanisms, whereby defective neural crest migration leads to second- 
ary anomalies in nearby ectoderm, have also been suggested for other defects associated with anterior segment dysgenesis, including umbilical hernia and hypospadias. The most cephalad extension of the neural crest, termed the “prosencephalic neural ridge,” also gives rise to both the hypothalamus and the pituitary, perhaps explaining the pituitary and neuroendocrine abnormalities that may occur in some patients with ARS. It may be, therefore, that most, if not all, anomalies associated with the anterior segment dysgenesis syndromes represent primary developmental disorders of the neural crest.

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