

Uveal Coloboma: The Related Syndromes

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Coloboma is a term derived from a Greek root, meaning mutilated or curtailed.¹ Optic nerve and retino-choroidal coloboma are caused by incomplete closure of the embryonic fissure during fetal development.¹ The incidence of coloboma is reported per 10,000 births to be 0.5 in Spain, 0.7 in France, and 0.75 in China.²⁻⁴ When isolated, coloboma is most commonly sporadic and can be inherited in an autosomal dominant, autosomal recessive, and x-linked recessive fashion.¹ Its predominant association with other congenital anomalies, however, highlights the genetic heterogeneity of this ocular malformation.

In this report, we discuss a family with multiple ocular malformations and emphasize the various disorders associated with chorioretinal coloboma.

THREE CASES FROM ONE FAMILY

Patient 1. A 3-1/2-month-old white male manifested left esotropia since birth. On examination, visual acuity was fix-and-follow in both eyes. Slit-lamp exam of both eyes disclosed bilateral leukocoria and 30 prism diopters of alternating esotropia (Figure 1A). There was no iris or lens coloboma and no nystagmus. Fundus evaluation revealed chorioretinal and optic nerve coloboma with sparing of fovea in both eyes (Figures 1B and 1C). Genetic testing revealed CHD-7 missense mutation, but systemic evaluation with chest x-ray, echocardiogram, and MRI was normal. At 1-year follow-up, the colobomata were stable in size and there was no retinal detachment.

Patient 2. A 2-month-old white female, born with

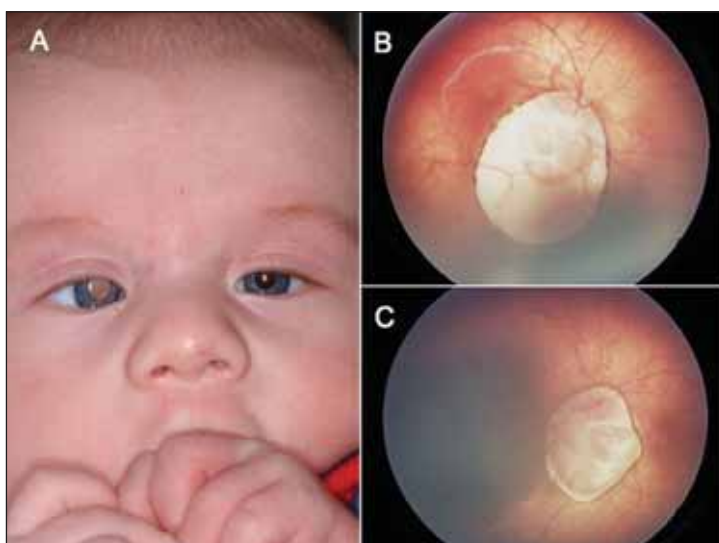


Figure 1. Patient 1. A 3-1/2-month old male presenting with strabismus and leukocoria was found to have bilateral chorioretinal colobomas. External photograph demonstrating right eye leukocoria and bilateral esotropia. There was no iris coloboma in either eye (A). Chorioretinal coloboma in the inferonasal quadrant of right eye measuring 10 x 9 mm that involves the optic disc sparing the fovea (B). Chorioretinal coloboma in the inferonasal quadrant of left eye measuring 7 x 7 mm that involves the optic disc (C).

cleft lip and palate (Figure 2A) was noted to have nystagmus from birth. Patient has a family history of coloboma in her brother (Patient 1) and optic nerve hypoplasia in mother (Patient 3). On examination, the right eye was microphthalmic and had two colobomata including a large optic nerve coloboma and a smaller macular coloboma (Figure 2B). Ultrasound evaluation revealed a small orbital cyst, contiguous with the coloboma. In the left eye, there was a single coloboma

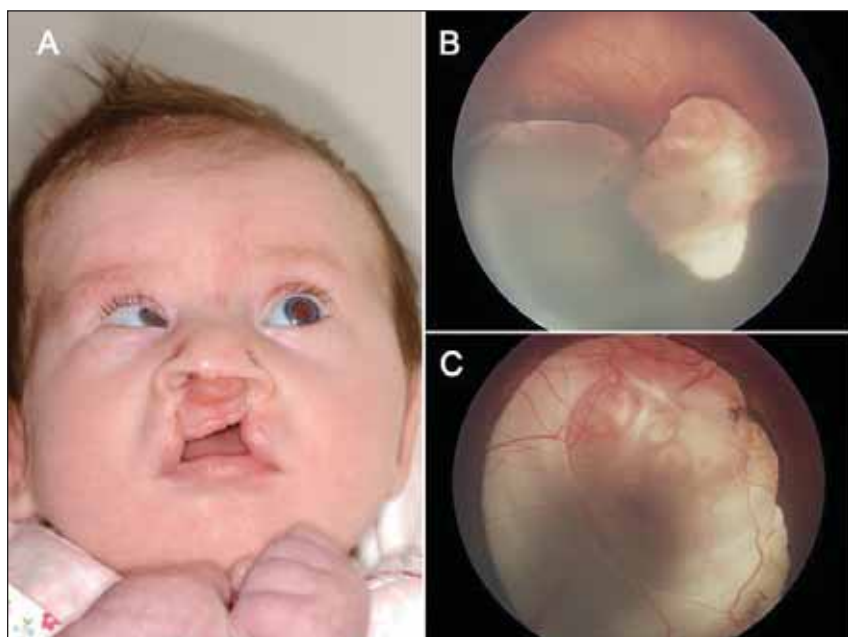


Figure 2. Patient 2. A 2-month-old female presented with bilateral chorioretinal colobomas, microphthalmos with cyst, and a cleft lip and palate. External photograph demonstrating right eye microphthalmos with esotropia and cleft lip (A). Right microphthalmic eye with two colobomas: a large optic nerve coloboma measuring 11 x 10 mm and a macular coloboma measuring 10 x 6 mm (B). Single coloboma seen inferonasally in the left eye measuring 19 mm in greatest diameter with involvement of the optic disc and the edge of the fovea (C).

inferonasally involving the optic disc and the edge of the foveola (Figure 2C). Genetic testing confirmed CHD-7 missense mutation. MRI of the brain showed that the brainstem, particularly the pons, was reduced in size.

Patient 3. The mother of patients 1 and 2 is a 33-year-old white female with a history of congenital cataracts, optic nerve hypoplasia, and multiple strabismus surgeries. On examination, the patient was legally blind and aphakic in both eyes. Fundus exam revealed bilateral optic nerve hypoplasia. The patient's brain MRI was within normal limits. Genetic testing revealed no chromosomal abnormalities.

DISCUSSION

Coloboma results from the failure of the optic fissure to close during the fifth to seventh week of gestation when the embryo corresponds to the 7-mm to 14-mm stage of development.¹ The timing of the defect explains the multiple associations with systemic malformations. Bermejo and associates³ evaluated 55 eyes with coloboma and found that coloboma occurred in isolation in 15% of cases, with multi-

ple congenital anomalies in 58%, and as part of a multisystem syndrome in 27%.

The most important coloboma-related syndromes are listed below.

CHARGE Syndrome (Hall-Hittner syndrome; OMIM 214800). This is the most common syndrome found in patients with coloboma.⁵ CHARGE syndrome occurs in almost 20% of patients with uveal coloboma.⁶ CHARGE syndrome includes the following features: coloboma, heart defects, atresia (choanae), retardation of growth and development, genitourinary problems, and ear anomalies. The incidence rate of CHARGE syndrome is 0.1 to 1.2 per 10,000 live births.⁷

CHARGE syndrome is a clinical diagnosis. An expert committee in 1998 formulated the diagnostic criteria for CHARGE syndrome. The major criteria are the classic 4C's, which

include 1) choanal atresia, 2) coloboma, 3) characteristic ears and 4) cranial nerve anomalies. The minor criteria include cardiovascular malformations, genital hypoplasia, cleft lip/palate, tracheoesophageal fistula, CHARGE facies, growth deficiency and developmental delay. Individuals with all four major characteristics or three major and three minor characteristics are highly likely to have CHARGE syndrome.⁸

Ophthalmic manifestations of CHARGE syndrome include uveal coloboma, optic nerve hypoplasia, microphthalmia, anophthalmia, nystagmus, strabismus, and refractive errors.⁹ In regard to genetics, CHD7 (chromodomain helicase DNA-binding protein) mutations are seen in two-thirds of cases.⁹

Renal Coloboma Syndrome (OMIM 120330). This abnormality is associated with progressive renal insufficiency needing dialysis and transplantation; hence, early diagnosis is critical. Ophthalmic manifestations include coloboma of the optic nerve and abnormal vascular pattern of the optic disc.¹⁰ The systemic manifestations include renal hypoplasia

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(leading to renal failure), vesicoureteral reflux, and sensorineural hearing loss.¹¹ In regard to genetics, renal coloboma syndrome is autosomal dominant. PAX2 gene mutations are seen in nearly 50% of patients.¹²

Cat-eye syndrome (Schmid-Fraccaro syndrome; OMIM 115470). Cat-eye syndrome is a rare disorder with classical triad of iris coloboma, anal anomalies, and preauricular malformations. Its systemic manifestations include preauricular tags, facial dysmorphism, anal atresia, congenital heart disease and urogenital malformation.¹³ Cat-eye syndrome features a supernumerary chromosome consisting of duplicated material of chromosome 22.¹³

Kabuki syndrome (OMIM 147920). This is an autosomal dominant disorder that is important to differentiate from CHARGE syndrome. Overlapping systemic features with CHARGE syndrome are coloboma, cleft palate, heart defects, and growth retardation. Unique features include long palpebral fissures with eversion of the lateral third of lower eyelids, sparse eyebrows, and large ears.¹⁴ This characteristic facies does not manifest until 2 to 4 years of age; hence, follow-up is essential to differentiate CHARGE syndrome from Kabuki syndrome.¹⁴ The genetic causes of Kabuki syndrome are unknown.

Miscellaneous syndromes. Other syndromes associated with coloboma include Walker-Warburg syndrome, Noonan syndrome, linear sebaceous nevus syndrome, focal dermal hypoplasia, Aicardi syndrome, and Goldenhar syndrome.¹⁵

SUMMARY

We have described two cases of CHARGE syndrome with documented CHD7 mutation in a brother and sister, whose presentations illustrate the phenotypic heterogeneity of this syndrome. Although they can occur in isolation, colobomata are commonly associated with other congenital ocular and systemic anomalies. The diagnosis of coloboma by an ophthalmologist should prompt a careful systemic workup and family history. ■

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