Ocular manifestations in a family with brachio-oculo-facial syndrome

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We report 3 siblings with brachio-oculo-facial syndrome (BOFS) who present with the predominant ocular phenotype. This syndrome has rarely been reported in multiple first-degree relatives.

Brachio-oculo-facial syndrome (BOFS) is a rare autosomal dominant congenital disorder that was first described in 1987 by Fujimoto and colleagues.[1] It is characterized by ocular abnormalities, including microcornea, iris coloboma, chorioretinal coloboma, and nasolacrimal duct obstruction; brachial abnormalities, including atrophic, or hemangiomatous cervical, or supracervical skin lesions; and craniofacial abnormalities, such as incomplete or complete cleft lip with or without cleft palate.[2] Deafness and temporal bone anomalies, renal malformations, and ectodermal abnormalities, such as premature graying of the hair and iris heterochromia can be present.[3] The gene mutation *TFAP2A* (transcription factor activating enhancer-binding protein 2-alpha) is responsible for BOFS.[4] We report a family of 3 children presenting with predominant ocular abnormalities and BOFS.

Case Reports

Patient 1

Patient 1 is an 11-year-old boy who was referred initially as a 7-year-old to Bascom Palmer Eye Institute for decreased vision in his right eye. On examination at age 7 his visual acuity in the right eye was counting fingers; in the left eye, 20/20. His intraocular pressure (IOP) was normal in both eyes. The right eye revealed microphthalmia, microcornea (diameter, 8 mm), axial length of 22.2 mm, cataract, and an iris and chorioretinal coloboma (Figure 1). There was no retrobulbar cyst on B-scan ultrasound. Examination of the left eye was unremarkable. The patient developed graying of his hair at age 5 years, and he had atresia of the left inner ear and a dysmorphic right external ear.

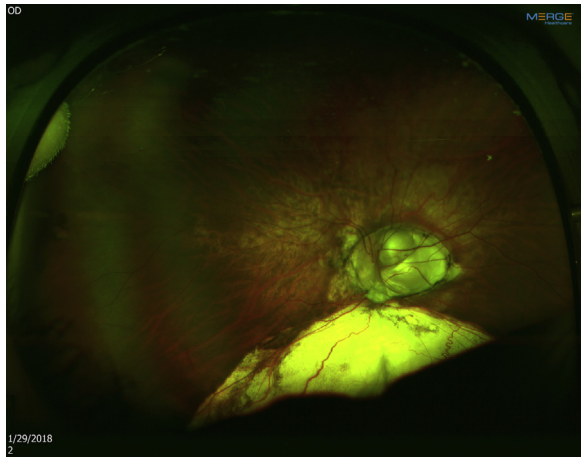

FIG 1. Chorioretinal and optic nerve coloboma in the right eye of patient 1 at age 11.

Patient 2

The 6-year-old brother of patient 1 was examined because of family history and found to have bilateral iris and chorioretinal coloboma. Visual acuity in his right eye was counting fingers; in his left eye, 20/400. IOP was normal in both eyes. The right eye had microphthalmia, microcornea (6 mm), axial length of 21.6 mm, iris coloboma, and chorioretinal coloboma involving the macula. Examination of the left eye revealed a corneal diameter of 10 mm, axial length of 25.1 mm, inferior iris coloboma with posterior synechiae, and chorioretinal coloboma, with an old choroidal neovascular membrane at the edge of the coloboma (Figure 2). B-scan ultrasonography revealed moderately dense vitreous opacities and an vitreoretinal adhesion to the intercalary membrane of the coloboma, with no retrobulbar cyst (Figure 2); B-scan ultrasonography of the left eye revealed mild vitreous opacities and marked posterior staphyloma and coloboma of the fundus with no retrobulbar cyst. He had genetic testing with microarray comparative genomic hybridization, which showed a ~3.01 Mb deletion resulting in 6p24.3 segmental loss, with the lost segment between (5′) 7,418,180 and (3′) 10,427,177 and causing a segment loss in the *TFAP2A* gene. He had a history of a patent ductus arteriosus but no ear or facial abnormalities.

Patient 3

The youngest sibling of the first 2 patients, a 15-month-old girl, was examined because of family history. She could fix and follow in both eyes. IOP was normal in both eyes. On examination, both eyes were microphthalmic (corneal diameter right eye, 8 mm; left eye, 7 mm). The right eye had an iris coloboma with persisting vessels and posterior

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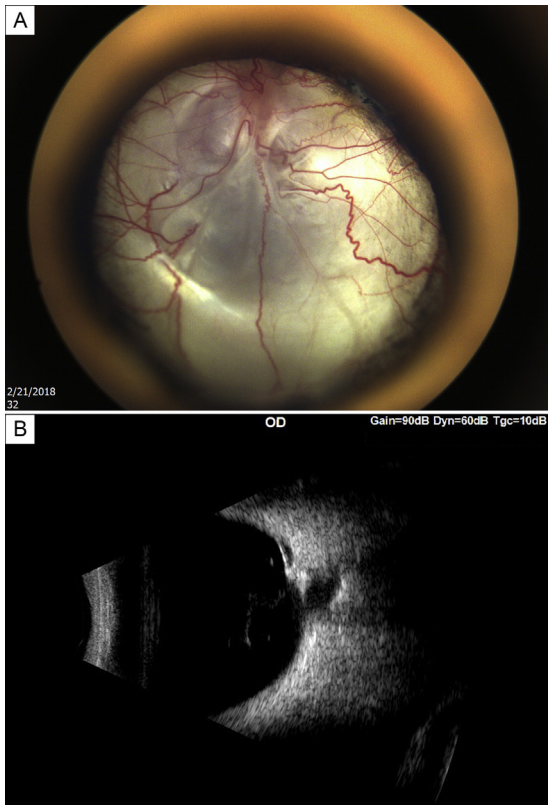

FIG 2. A, Chorioretinal coloboma in the left eye of patient 2. B, B-scan ultrasound of the right eye of patient 2 showing intercalary membrane.

synechiae, a cortical lens opacity off the visual axis, axial length of 16.4 mm, and a chorioretinal coloboma (Figure 3). The left eye showed similar findings, with an iris coloboma and iris-to-lens adhesion at 4 o'clock, with suspected small anterior capsular opacity, axial length of 19.6 mm, and chorioretinal coloboma. B-scan ultrasonography of the right eye revealed a retinal detachment from near the equator to posterior to the equator in the temporal quadrant. There was bilateral coloboma of the optic nerve head and a retrobulbar cyst on the right. There was no mass lesion or fundus calcification detected in either eye. She had a history of cleft palate repair.

The mother had a normal ocular examination with no retinal findings but had facial findings of a pseudocleft lip, previous neck surgery for a brachial cleft abnormality, external ear dysmorphia, and early graying of the hair, which started in her twenties.

Discussion

Ocular abnormalities are often present in patients with BOFS, with 83% of cases reported involving the eye.[3] The most frequently encountered ocular anomalies include microphthalmia, coloboma, and nasolacrimal duct obstruction.[3] Our 3 patients met the diagnostic requirements by having 2 of the 3 main features (cervical skin defects, ocular anomalies, facial anomalies) and a first-degree affected relative.[4]

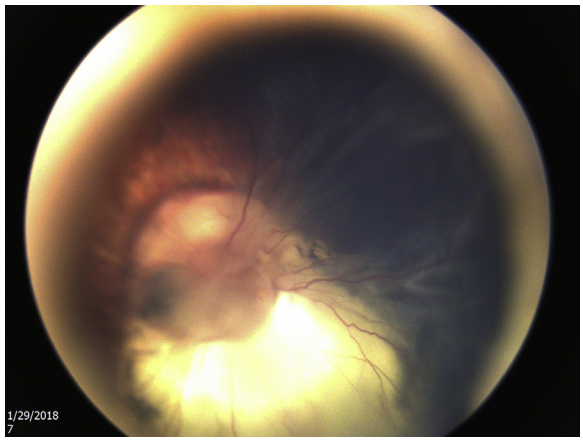

FIG 3. Chorioretinal coloboma right eye of patient 3.

The youngest sibling was found to have a retinal detachment associated with coloboma and retrobulbar cyst. This finding is consistent with the reported association of retinal coloboma and retinal detachment. There is an increased risk of retinal detachment with coloboma, with a prevalence of about 40%.[5] Retinal detachments are common and have a worse prognosis, given the lack of pigmentation at the site of choroidal coloboma, abnormally thin retina, presence of staphyloma, thin sclera, and involvement of the optic disk and macula.[5,6] Furthermore, retinal detachment is more likely in eyes with retrobulbar cysts.[7] Retinal detachment surgery associated with coloboma is more challenging than in the general population, with a success rate of about 81.2% after 13 months, with most cases requiring silicone oil.[8] Surgical management was discussed with the family for the youngest sibling (patient 3) with retinal detachment, and after discussion of the benefits and risks the family decided on conservative management.

TFAP2A is part of the AP-2 transcription factor family and involved in organogenesis.[4] One explanation for the varied phenotypes in BOFS was proposed by Gestri and colleagues,[9] who found that mutations in genes encoding for *bmp4* or *tcf7l1a* affected the penetrance and expressivity of *TFAP2A*. Somatic mosaicism has been found in a family with phenotypic variation and may help to explain these finding.[10] Patient 2 in this study had segment loss of 6p24.3, which is described in other cases of BOFS.[4] The chromosomal deletion is in the same location as the previously reported cases by Milunsky and colleagues[4] that lead to the discovery of the *TFAP2A* gene associated with BOFS. In this previous report the son had a short and tented prominent philtrum.[4] In contrast, the youngest sibling in our series had a history of cleft palate repair.

Given the varied expression of BOFS, genetic testing can be useful in cases of mild phenotype and can provide families with a diagnosis and lead to genetic counseling. There is variability within families of BOFS, which warrants

molecular testing of parents for more accurate recurrence risk counseling.[4]

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Management of orbital rhabdomyosarcoma in a child with Li-Fraumeni syndrome

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This case highlights the management of orbital rhabdomyosarcoma in a child with Li Fraumeni syndrome (LFS). Treatment with chemotherapy and eventual orbital exenteration enabled margin-free control of the tumor. Radiation therapy was avoided to reduce the risk of inducing additional malignancy. Reactive orbital hyperostosis was observed postoperatively and was confirmed with surgical biopsy of the orbital roof. In this case, systemic surveillance imaging, which is necessary in patients with LFS, revealed an adrenal cortical carcinoma.

An 18-month-old-boy presented with a 5-week history of nontender, progressive right periorbital swelling (Figure 1A). Examination showed fullness of the right upper eyelid, proptosis, and hypoglobus with limited supraduction. He was otherwise well, with no evidence of fever or systemic illness. Maternal family history was significant for brain, esophageal, and breast cancer.

Magnetic resonance imaging (MRI) with gadolinium demonstrated a multilobulated right orbital mass that involved both intraconal and extraconal spaces surrounding and displacing the right globe anteriorly and occupying the anterior superior and medial aspects of the orbit (Figure 1B). The lesion was isointense to muscle on T1-weighted images with heterogeneous enhancement. There was erosion of the lateral margin of the orbit without intracranial extension.

An incisional biopsy confirmed a diagnosis of rhabdomyosarcoma with anaplasia. A focal nesting pattern of reticulin staining suggested the alveolar histologic subtype. Immunohistochemistry did not demonstrate either the t(1:13)(p36:q14) or t(2;13)(q35;q14) reciprocal translocations typical of alveolar histology, although 23% of alveolar rhabdomyosarcoma may be PAX-fusion negative.[1] Bone marrow biopsies showed no evidence of malignant infiltration. Genetic testing of the patient and his mother revealed heterozygosity for a *TP53* germline mutation (exon 8: c.880dup [p.Glu294fs]), confirming the diagnosis of Li-Fraumeni syndrome.

Orbital radiation was avoided because of the risk of inciting a secondary malignancy. The patient received neoadjuvant chemotherapy with vincristine, dactinomycin, and cyclophosphamide, according to the Children's Oncology Group ARST0331 protocol for low-risk RMS. Subsequent neuroimaging studies demonstrated a reduction in the tumor size. After undergoing a surgical debulking procedure elsewhere that did not provide margin-free control, he underwent a right orbital exenteration. Histopathological examination showed residual viable rhabdomyosarcoma with features of rhabdomyoblastic/cytic maturation. The margins of resection were tumor free. To enable postoperative monitoring, no reconstructive flap was placed over the bone. Subsequent postoperative examinations demonstrated a healing right orbital socket, with no evidence of discharge or recurrence.

Four months after exenteration, computed tomography revealed expansion of the right orbital roof (Figure 2A). Suspicion was raised for tumor recurrence or a second primary malignancy such as osteosarcoma. Biopsy of the right orbital roof was aided by intraoperative imaging

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