Retinal Hamartoma in Oral-Facial-Digital Syndrome

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Only recently have intraocular findings been described in oral-facial-digital syndrome (OFDS), including 5 cases of chorioretinal colobomas and 1 case of optic nerve coloboma. We report a case of a new ocular anomaly associated with this syndrome: a retinal hamartoma in a male infant with OFDS. The patient had bilateral retinal masses that were suspicious for retinoblastoma because of a family history of retinoblastoma. Physical examination and imaging studies of the retinal masses could not differentiate between retinoblastoma, hamartoma, or persistent hyperplastic primary vitreous. Subsequent pathologic study of an enucleated globe was diagnostic of a retinal hamartoma. This case further illustrates the heterogeneity of ocular anomalies in OFDS and underscores the importance of a complete ophthalmologic evaluation in patients with this syndrome.


Oral-facial-digital syndrome (OFDS) describes a group of syndromes characterized by congenital anomalies of the oral cavity (cleft palate, tongue hamartomas, bifid tongue, multiple hyperplastic frenula), face (hypoplastic nasal cartilage), and digits (syndactyly, polydactyly, brachydactyly, clinodactyly). Ophthalmologic findings that have been reported in OFDS include hypertelorism, strabismus, and seesaw winking. Only recently have intraocular findings been reported, including 5 cases of chorioretinal colobomas and 1 case of optic nerve coloboma. However, ocular findings in most cases of OFDS have not been well documented, and ocular manifestations of OFDS are still not well described in the ophthalmologic literature. Here we report a case of an ocular finding not previously described in OFDS, a case of an infant with OFDS and a family history of retinoblastoma who was originally seen with bilateral retinal masses.

REPORT OF A CASE

A full-term male infant was referred to us because of suspected bilateral retinoblastoma. This was the first pregnancy of a mother with a history of unilateral retinoblastoma who was otherwise phenotypically normal. Both the parents and the paternal grandparents were first cousins. Pregnancy was without complication, and the infant was delivered at 39 weeks gestation. The infant was initially mildly hypotonic but quickly improved. Physical examination and subsequent genetic evaluation revealed multiple congenital anomalies consistent with OFDS, including multiple tongue hamartomas, corrugated gingiva, short flat bridge of nose, and bilateral polydactyly of the hands and feet (Figure 1, Figure 2, and Figure 3). Other considerations included in the differential diagnosis were retinoblastoma, persistent hyperplastic primary vitreous, and Norrie’s disease.

Ophthalmologic examination was performed at the University of California, San Francisco, when the infant was 10 days old. The infant exhibited hypertelorism and bilateral blepharophimosis. It could not be determined whether he had any useful vision. The iris was dysmorphic with irregular borders in both eyes. Also in both eyes was a retinal yellow-white mass with overlying hemorrhage. No evidence of normal retinal vasculature was associated with the masses. Ultrasonography demonstrated a solid mass without
intrinsic calcification. A computed tomographic scan of the orbits showed bilateral intraocular masses without the calcifications typical of retinoblastoma. The scan also revealed small optic nerves bilaterally. It could not be determined whether the masses represented retinoblastoma, hamartomas, or some variant of persistent hyperplastic primary vitreous. It was the recommendation of the Pediatric Tumor Board, University of California, San Francisco, to maintain close observation with eye examinations performed under anesthesia every few weeks. If the retinal masses did not change, observation would continue; if the masses began to grow or calcify, enucleation of the worse eye would be performed for treatment and diagnosis.

At 2 months of age, a computed tomographic scan of the orbit demonstrated no further growth of the masses but did indicate new calcification in the right eye, consistent with the diagnosis of retinoblastoma. At the time of enucleation, the infant exhibited no fixation or following behavior. Ophthalmic examination revealed a completely flat anterior chamber in the right eye and a formed chamber with some synechiae in the left eye. Pneumotonometry showed elevated pressures bilaterally, with 28 to 29 mm Hg OD and 24 to 25 mm Hg OS. Corneal diameters were also increased bilaterally: 11.5 mm vertically and 11.0 mm horizontally in the right eye, and 9.0 mm vertically and 9.0 mm horizontally in the left eye. Medical treatment of the glaucoma was instituted. Enucleation of the right eye with placement of a prosthesis was performed without complication.

Pathologic examination of the enucleated right eye revealed a total retinal detachment in a funnel configuration with eosinophilic exudate filling the subretinal space. The retinal layers were disorganized with areas of dysplasia (Figure 4 and Figure 5). These findings were consistent with a retinal hamartoma. In
addition, pathologic studies also demonstrated an iris in apposition to the corneal endothelium producing apposition angle closure. The optic nerve was atrophic with no evidence of neoplastic invasion. No calcification or retinoblastoma was seen.

Cytogenetic testing revealed normal chromosomes by G-band analysis.

**COMMENT**

Oral-facial-digital syndrome was first described by Papillon-League and Psaume in 1954, and since then, up to 9 distinct types of OFDS have been described. Ocular findings that have been described include hypertelorism in types I, II, III, IV, and VI; strabismus in I, II, and IV; and saw-winking in type IV.1 Recently, a new type (originally described as type VIII, but reclassified as type IX) has been described as a variant of type II associated with retinal abnormalities.2 To date, this new type IX has been the only type associated with intraocular findings. However, it is unclear whether complete ophthalmologic examinations were performed on the early reported cases of OFDS; intraocular anomalies therefore cannot be excluded in other types of OFDS. Our patient has findings most consistent with OFDS type IX. To date, only 6 prior cases of OFDS type IX have been reported, including 5 cases of chorioretinal colobomas and 1 case of optic nerve coloboma. To our knowledge, retinal masses, such as the ones in our patient, have never been reported in OFDS.

Because of the lack of precedent, it was uncertain initially if our patient’s bilateral retinal masses were hamartomas and if this type of hamartoma was even consistent with OFDS. Because our patient’s mother had a history of unilateral retinoblastoma, the possibility that the retinal masses were retinoblastoma was also very likely. Patients with unilateral retinoblastoma have a reported 15% risk of germline mutation. Ophthalmologic examination and imaging studies also raised the possibility of persistent hyperplastic primary vitreous and Norrie’s disease. Because the right retinal mass later developed some calcification, which was most consistent with a diagnosis of retinoblastoma, enucleation of the right eye was performed. Only after pathologic evaluation of the globe was the final diagnosis of hamartoma determined. However, the appearance of the left eye (Figure 6) and subsequent clinical course may be more consistent with persistent hyperplastic primary vitreous in that eye.

To our knowledge, this article reports the first case of OFDS associated with retinal hamartoma. Because of many prior reported cases of ocular anomalies associated with OFDS, it is likely that our patient’s ocular anomalies are related to his OFDS rather than being just coincidental findings. This case further illustrates the heterogeneity of ocular anomalies in OFDS and underscores the importance of a complete ophthalmologic evaluation in patients with this syndrome.

Accepted for publication December 26, 1998.

We are grateful to Sharon Wheeler for her editorial comments.

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**REFERENCES**


Figure 6. Fundus photograph of posterior pole in the left eye, taken through the central cataractous lens, demonstrates a central yellow-white mass possibly consistent with persistent hyperplastic primary vitreous.