



Case report

Familial exudative vitreoretinopathy presentation as persistent fetal vasculature

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ABSTRACT

Purpose: To illustrate a presentation of familial exudative vitreoretinopathy (FEVR) that can be mistaken for persistent fetal vasculature (PFV) and the importance of wide angle fluorescein angiography in making this distinction. A patient was referred with a unilateral retrolental membrane and retinal detachment from PFV but was found to have FEVR.

Observations: A 4 month-old full-term infant was referred with the diagnosis of PFV based on findings of a dense retrolental membrane and microphthalmia in the left eye. The patient had a near-complete retinal detachment with some exudation. Wide-field fluorescein angiography of the right eye revealed avascular retina and leakage at the vascular/avascular junction. Genetic testing confirmed a mutation in *FZD4*, supporting the clinical diagnosis of FEVR. Prompt laser therapy to the avascular area in the right eye was performed and lensectomy/vitreotomy with membrane dissection was performed in the left eye.

Conclusions and importance: FEVR can present with great variability between eyes. In patients presenting with findings suggestive of PFV, careful bilateral examination with wide-field fluorescein angiography is helpful. Early diagnosis and treatment are important to preserve visual acuity, especially in the less affected eye.

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1. Introduction

Familial exudative vitreoretinopathy (FEVR) was first described in 1969 by Criswick and Schepens as an inherited condition with wide variability of expressivity.¹ In mild cases of the disease, peripheral retinal avascularity is observed much like retinopathy of prematurity, but patients lack a history of preterm delivery and neonatal oxygen exposure. Patients with mild disease may not experience progression, but some eyes will develop neo-vascularization and exudation following asymptomatic periods.² In more severe stages of disease, reported presentations include subretinal and intraretinal exudates with retinal detachments, macula ectopia, epiretinal membranes and retinal folds.¹ The phenotypic expression of FEVR can differ greatly in eyes of the same individual, but some evidence of disease is often present bilaterally.³

Persistent fetal vasculature (PFV) has been described as an idiopathic congenital malformation in which the hyaloid artery fails

to regress and resorb during development, resulting in intraocular fibrovascular remnants.⁴ The disease is most commonly unilateral, although associated genetic conditions with bilateral findings have been reported prior to wide-angle imaging or genetic testing.⁵ The initial presentation of PFV includes the discovery of retrolental tissue, microcornea, and microphthalmos in severe anterior cases. Additional posterior segment findings include retinal and optic nerve hypoplasia and macular anomalies. Disease progression is associated with secondary glaucoma, intravitreal hemorrhage, retinal detachment and amblyopia.⁴

We describe an infant referred for PFV because of unilateral microphthalmia and leukocoria, who was subsequently found to have FEVR with highly dissimilar findings between eyes. We present findings of wide-angle fluorescein angiography that helped in the diagnosis.

2. Case report

A 4-month old boy born at full term after an uncomplicated pregnancy presented with exophoria and microphthalmia of the left eye with right eye preference to the referring pediatric

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ophthalmologist. The patient was diagnosed with unilateral leukocoria and probable PFV. The infant was referred to the pediatric retina service for management. Past medical history was unremarkable. The family history was positive for strabismus in the mother and congenital cataract of unknown etiology in a maternal uncle.

On initial examination, the infant was able to fix and follow with both eyes. He had a mild afferent pupillary defect in the left eye. Corneal diameters were 11 mm OD and 10 mm OS. External examination was otherwise normal bilaterally. Fundus exam of the right posterior pole was normal, but no view of the retina was possible on the left eye because of a dense retrolental membrane. A B-Scan ultrasound was performed, which showed a total retinal detachment with an open funnel. The decision was made to proceed with examination under anesthesia (EUA) in both eyes and possible lensectomy and vitrectomy in the left eye.

On EUA, scleral depression with indirect ophthalmoscopy revealed seven clock-hours of peripheral avascular retina temporally in the right eye. Fluorescein angiography delineated peripheral avascular retina and identified leakage of the vessels at the junction of vascular and avascular retina consistent with stage 2A FEVR (Fig. 1). The optical coherence tomography of the right eye was normal (Fig. 2). The patient underwent lensectomy and vitrectomy in the left eye of the retrolental membrane from Stage 5A FEVR (Fig. 3). The patient underwent scatter photocoagulation of the avascular retina in the right eye (Fig. 4). Subsequent surgeries to drain subretinal fluid or release traction were performed in the left eye. The right eye showed less leakage on fluorescein angiography and remained stable. Genetic studies revealed a heterozygous mutation of the *FZD4* gene via the eyeGENE[®] research study.

At age 21-months, disease in the right eye remained stable after scatter photocoagulation. The left eye showed partial reattachment of the retinal detachment with resolving subretinal exudates and a persistent subretinal band and nasal fold (Fig. 5). Current management includes regular monitoring, protective eyewear and maximizing visual outcome in both eyes, as well as eye examinations of family members for FEVR.

3. Discussion

FEVR can be inherited in autosomal dominant, autosomal recessive, and X-linked recessive ways. Mutations in *FZD4*, *LRP5*, *NDP* and *TSPAN12*, members of the Wnt signaling pathway, are implicated in about 50% of cases.⁶ Newly discovered mutations in

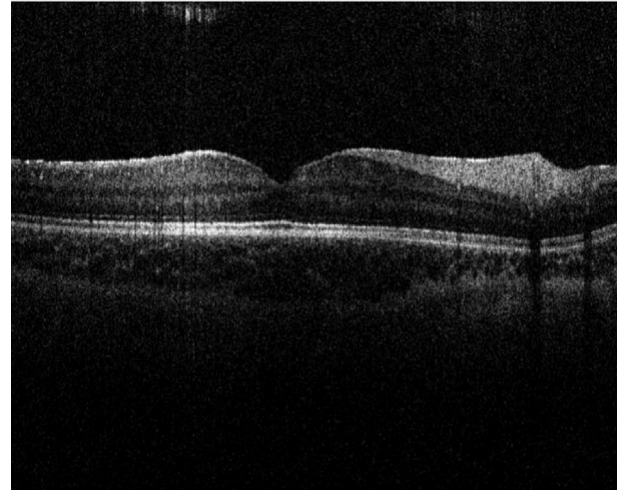


Fig. 2. Optical coherence tomography (OCT) of the right eye. Normal retinal layers are observed, with no intraretinal fluid or exudates.

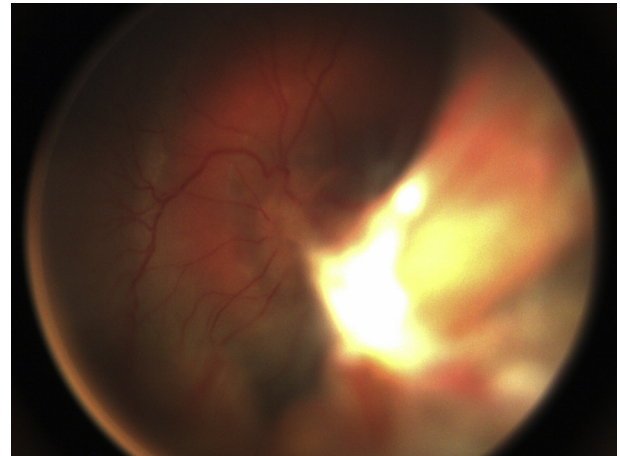


Fig. 3. Fundus image of the left eye at 4 months, following initial lensectomy-vitrectomy. A nasal retinal fold is observed from the surgeon's view, as well as a circumferential subretinal band surrounding the optic nerve.

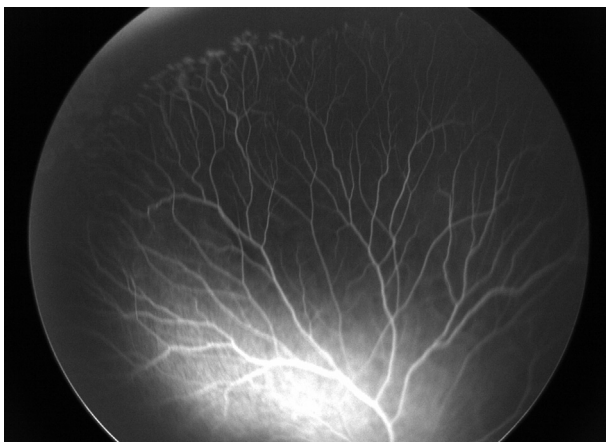


Fig. 1. Fluorescein angiography (FA) of the right eye. There is an area of peripheral avascular retina with neovascular tufts along the border.

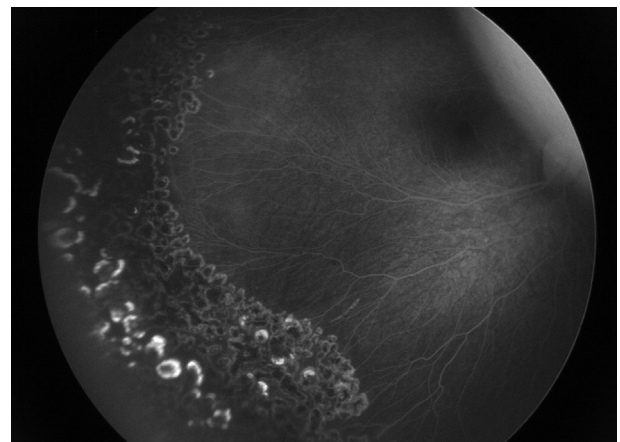


Fig. 4. Fluorescein angiography (FA) of the right eye. Scatter photocoagulation has been performed to include the avascular retina and neovascularization in its entirety.

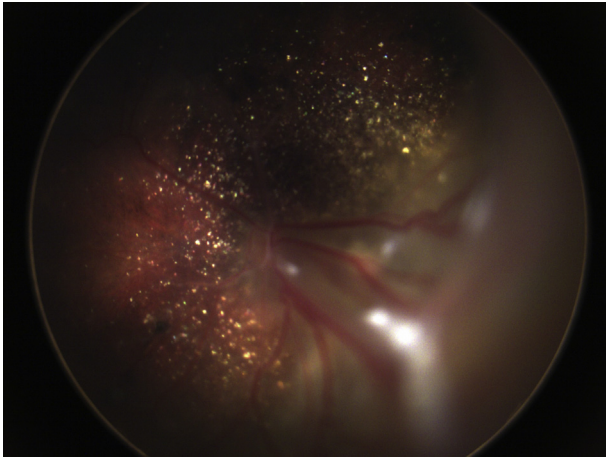


Fig. 5. Fundus image of the left eye at 21 months. Intra-retinal cholesterol crystals remain after some resolution of exudates. A sub-retinal band with persistent exudates is observed extending anteriorly.

ZNF408 have also been shown to lead to disease.⁷ Expressivity is variable, and patients can present with widely different appearances between eyes as presented in this case.³ The disparity of presentation between the eyes can make the distinction between FEVR and other unilateral pediatric diseases, such as PFV, difficult to make, leading to incorrect or incomplete treatment. The reasons for the disparity in presentation are largely unknown, but may relate to different temporal effects of the pathophysiology from the same molecular defect and/or from variable expressivity in different cells at different stages of development within the eye, as examples.

FEVR has been classified by the following stages: Stage 1 is a retinal avascular zone without neovascularization; Stage 2 is avascular retina with neovascularization at the junction of vascular/avascular retina and further delineated by the presence (stage 2A) or absence (stage 2B) of intraretinal or subretinal exudates; Stages 3 and 4 are subtotal retinal detachments based on foveal involvement; Stage 5 disease is total retinal detachment.⁸ An estimated 6% of patients present with retinal folds extending from the posterior pole to the lens.⁹ The overlap of FEVR and PFV has been described.^{1,10} This case highlights that FEVR can be present when one eye is smaller than the other, a characteristic often ascribed to PFV.

It is important for an infant with a retinal detachment in one eye to undergo careful ophthalmologic and retinal evaluations in both eyes with scleral depression. Wide field fluorescein angiography is helpful to detect leakage that is not clinically apparent or suspected in eyes without exudation. Laser therapy to avascular retina in Stage 2 FEVR is recommended. Retinal detachments are managed surgically, with frequent follow-up for monitoring of repeat detachments.⁸ Untreated FEVR, even in mild forms of disease, has the possibility of progression to exudative retinal detachments or retinal folds and severe visual compromise at older ages.²

Our case shows that FEVR can manifest with great variability between eyes in the same individual, even with asymmetry in

ocular size and corneal diameter that strongly suggest PFV. Visual acuity can be preserved with prompt therapy in the less affected fellow eye in highly asymmetric cases such as presented.

4. Patient consent

Patient consent was not obtained as all identifying patient information has been removed.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship. JZK drafted the initial report and approved the final version to be published. MEH conceptualized the report, revised the initial drafts, and approved the final version to be published.

Conflict of interest

The following authors have no financial disclosures: JZK, MEH.

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