

Update on FEVR: Diagnosis, Management, and Treatment

This lifelong disease requires prompt treatment and vigilant follow-up.

BY FRANCO M. RECCHIA, MD

Familial exudative vitreoretinopathy (FEVR) was first described in 1969 as a condition with fundus changes similar to those in retinopathy of prematurity, but appearing in children who had been born full-term with normal birthweight.^{1,2} Although this axiom is still accurate, we have made considerable progress in our ability to diagnose and treat FEVR in the more than 40 years since its description. This short article presents an update on current thinking about FEVR, especially as it relates to diagnosis, the use of widefield angiography, and treatment, and includes several practical take-home points that can aid us when we

see these patients in our practices.

FEVR is usually bilateral and asymmetric. It can present at any age, and the mean age of presentation is 6 years. The main hallmark of FEVR is an avascular peripheral retina with subsequent dragging of the vessels, with or without retinal folds, as well as preretinal, intraretinal, or subretinal exudation (Figure 1). This may lead to retinal detachment due to traction, exudation, a retinal tear, or a combination of these factors. FEVR may be associated with high myopia, anisometropic amblyopia, and cataract.

Pendergast and Trese developed a classification scheme for

FEVR based on clinical features (Table 1).³ It begins with peripheral avascularity in stage 1, advancing to preretinal neovascularization (stage 2), and then retinal detachment in varied forms, with or without exudation. This scheme is helpful to assess disease, organize studies, and guide treatment.

GENETIC ASSOCIATIONS

In recent years, some of the genetic associations of FEVR have been identified⁴⁻¹²; about 50% of cases can be linked to 4 causative genes (NDP, LRP5, FZD4, and TSPAN12), all of which form part of the Wnt signaling pathway, which is vital for normal retinal vascular development. Any abnormality in 1 of these genes may lead to disorders of retinal vasculogenesis.



Figure 1. Typical clinical features of FEVR include macular dragging, retinal folds, exudation, peripheral nonperfusion, retinal neovascularization, and retinal detachment.

TABLE 1. CLASSIFICATION OF FEVR

Stage	Clinical Features
1	Avascular retinal periphery
2	Preretinal neovascularization a – without exudate b – with exudate
3	Macula-sparing retinal detachment a – without exudate b – with exudate
4	Macula-involving retinal detachment a – without exudate b – with exudate
5	Total retinal detachment

Adapted from Pendergast SD, Trese MT.³

It appears that the type and number of mutations play a role in the severity of the disease.

Genetic information can be useful for unequivocal confirmation of diagnosis and for screening at-risk relatives, as well as for genetic counseling. Tests are available for all 4 genes implicated in FEVR, either through commercial

vendors or through eyeGENE, the National Ophthalmic Disease Genotyping Network, an initiative sponsored by the National Eye Institute (<http://www.nei.nih.gov/resources/eyegene.asp>).

NATURAL HISTORY

Benson compiled the classic review of the natural history of FEVR almost 2 decades ago.² Like many pediatric diseases, FEVR is most severe, and the prognosis is most guarded, in the youngest children, particularly those under age 3 years. Typically there are long periods of disease inactivity punctuated by episodes of reactivation. Detachment can occur up to 20 years after apparent disease stabilization. Even in adolescents and adults, disease that appears less severe on presentation can progress to more severe disease years later.

This leads to the first take-home point of this article:

FEVR is a lifelong disease requiring long-term follow-up and regular examinations. These children must be seen into adolescence and even into adulthood, so patients may be with you for life.

ROLE OF ANGIOGRAPHY

FEVR is a vascular disease, and therefore fluorescein angiography (FA) is invaluable to establish diagnosis and follow patients. Because many signs appear in the peripheral retina, widefield FA is particularly useful. Widefield FA can demonstrate typical retinal vascular findings including peripheral retinal nonperfusion, vessel pruning, avascularity, neovascularization, straightening of vessels, and peripheral vascular anastomoses (Figure 2). It can be helpful to detect cases in which the disease is suspected but not confirmed and in relatives of patients with FEVR (Figure 3).

Importantly, FA is also useful to guide treatment and to ensure that it is complete and accurate. FA helps to identify the border between vascular and avascular retina much better than fundus visualization alone. It also helps us to identify “skip” areas—areas of nonperfusion after apparently complete retinal ablation (Figure 4).

Take-home point No. 2: Angiography is essential for accurate diagnosis and successful treatment of patients with FEVR.

TREATMENT OPTIONS

Treatment of FEVR should be guided by the stage of disease. In stage 1 eyes with minimal



Figure 2. Fluorescein angiography shows typical retinal vascular findings of telangiectasias, vessel straightening and anastomoses, peripheral nonperfusion, and retinal neovascularization.

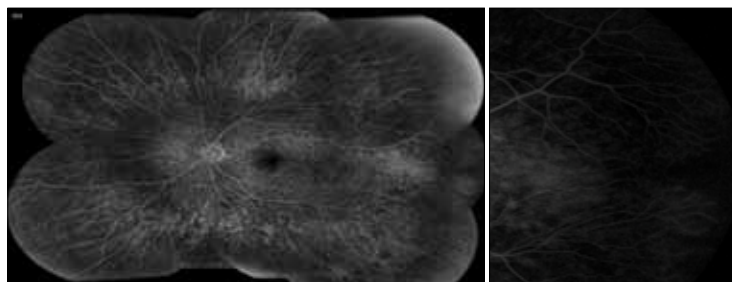


Figure 3. Case example: This asymptomatic patient has a niece with FEVR. Although clinical exam was unremarkable, peripheral angiography revealed areas of nonperfusion, straightening and trifurcation of vessels. A very mild form of FEVR is suspected. Of practical value, these findings suggest that we should examine and follow his 2 young daughters closely.

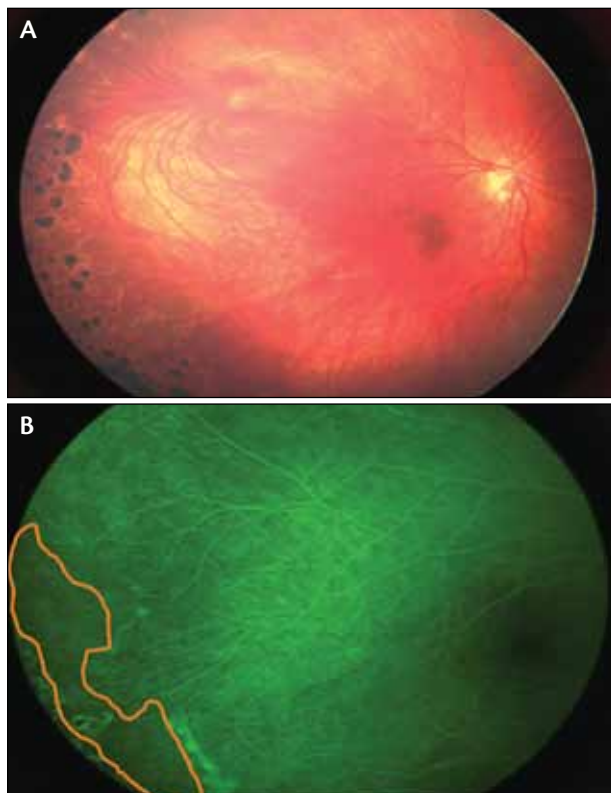


Figure 4. Another case example. This 18-month-old girl has FEVR associated with a large deletion of chromosome 11. In her blonde fundus, vessel landmarks are difficult to see, and laser appears adequate (A). However, fluorescein angiography reveals small skip areas of untreated avascular retina with fine fronds of neovascularization at their posterior borders (B).

peripheral avascularity, observation is reasonable. Peripheral retinal ablation may be called for in some cases, especially if a fellow eye has poor vision. In stage 2 (neovascularization with or without exudation), complete retinal ablation of all areas of peripheral retinal nonperfusion is recommended, typically with laser photocoagulation (Figure 5). For stages 3 to 5, depending on the configuration and stage of the detachment, vitrectomy with or without scleral buckling can be useful.

When surgery is considered, one must remember the unique aspects of pediatric eyes. The posterior hyaloid is tightly adherent; it does not strip easily mechanically. Because of the ischemic peripheral retina, manipulation of the adherent vitreoretinal interface may lead to atrophic breaks. And proliferative vitreoretinopathy (PVR) is common in pediatric eyes with open retinal breaks. Vascular activity and intraocular inflammation at the time of surgery are also frequently encountered.

Vitrectomy is helpful to address all vectors of vitreoretinal traction (Figure 6). It can be used alone when detachments



Figure 5. Montage fundus fluorescein angiography of the left eye of a 2-year-old child with FEVR. Despite previous peripheral laser photocoagulation to clinically visible avascular retina, angiography reveals peripheral nonperfusion and buds of preretinal neovascularization.

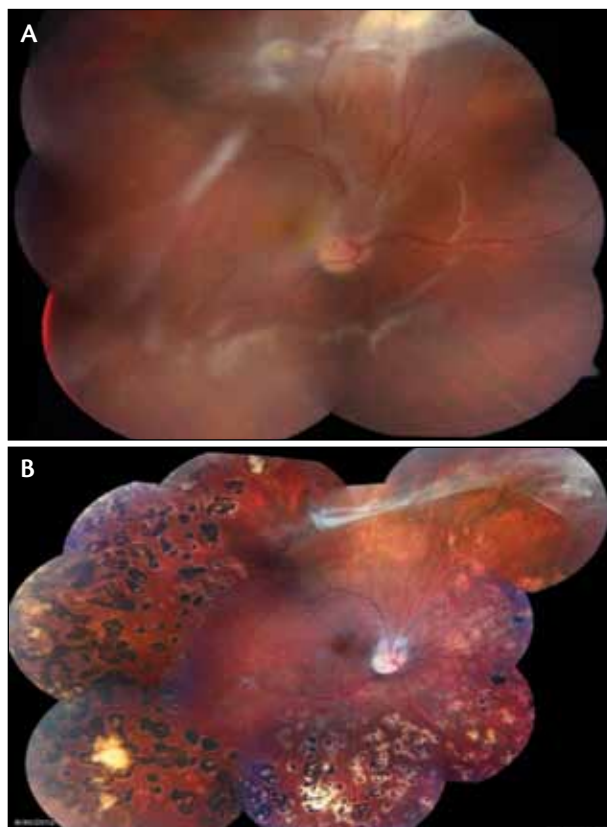


Figure 6. Montage color fundus photograph of an eye with combined traction-exudative retinal detachment in patient with FEVR (A). The same eye, 2 years following vitrectomy and laser photocoagulation for retinal detachment. Visual acuity has improved to 20/25 (B).

are predominantly tractional or exudative. In detachments with rhegmatogenous components, a broad scleral buckle may be helpful to support the vitreous base and peripheral ischemic retina and breaks. Internal drainage of subretinal fluid should be avoided to reduce the chance of PVR. Anti-VEGF agents can be helpful for initial containment of the disease or to reduce vascular activity in advance of surgery. However, anti-VEGF agents should not be used as monotherapy because their effect is transient and they do not address the underlying chronic ischemia.

Numerous reports of the results of vitreoretinal surgery for FEVR-associated retinal detachment have been published.^{3,13-16} In most cases (62–100%) macular attachment can be achieved. Visual acuity is stabilized or improved in 63% to 96% of cases, and roughly one-third require more than 1 surgery.

The final take-home point: Prompt retinal ablation of all avascular retina and vigilant follow-up are crucial to ensure treatment success.

SUMMARY

- FEVR is a lifelong disease requiring regular examinations.
- Angiography is essential for accurate diagnosis and successful treatment.
- Prompt treatment and vigilant follow-up are crucial for long-term success. ■

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