Familial Exudative Vitreoretinopathy (FEVR)

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INITIAL PRESENTATION

Chief Complaint: Bilateral retinal detachments

History of Present Illness:

A 48-day-old boy was referred for evaluation of bilateral retinal detachments. The pregnancy had been complicated by intrauterine growth restriction with a birth weight of 2.6kg. The infant was otherwise healthy. He was first noted to have abnormal red reflexes, non-reactive pupils, and pale discs with concern for overlying vascular abnormalities when evaluated by an outside pediatric ophthalmologist on day 8 of life. An outside retinal surgeon diagnosed bilateral, macula-involving tractional retinal detachments and performed same-day, bilateral lens-sparing vitrectomies. He was seen at the University of Iowa 1 month after surgery. Given his history, an examination under anesthesia (EUA) was performed.

Past Ocular History:

Bilateral tractional retinal detachments, status post lens-sparing vitrectomies

Medical History:

- Born at 37 weeks and 5 days gestation via uncomplicated, spontaneous vaginal delivery
- Intrauterine growth restriction

Medications:

Cholecalciferol

Allergies:

No known allergies

Family History:

Unremarkable

Social History:

Unremarkable

Review of Systems:

Unremarkable other than as noted in history of present illness.

OCULAR EXAMINATION

- Visual Acuity with correction:
  - Right eye (OD): No wince to light
  - Left eye (OS): No wince to light

- Ocular Motility/Alignment:
  Orthophoric by Hirschberg testing with low amplitude, conjugate nystagmus in the horizontal plane.

- Intraocular Pressure (IOP):
  - OD: 10 mmHg
  - OS: 9 mmHg

- Pupils:
  - OD: Non-reactive
  - OS: Non-reactive

- Confrontation visual fields:
  - OD: Too young to assess
  - OS: Too young to assess

- B-Scan Echography at presentation (Figure 1):
  - OD: No obvious membranes, localized shallow inferior retinal detachment
  - OS: Hyperechoic membranous elevation inferiorly and temporally consistent with retinal detachment

- Electroretinography:
  - OD: Non-recordable. Possibly due to young age versus retinal disease.
  - OS: Non-recordable. Possibly due to young age versus retinal disease.

- External:
  Normal, both eyes (OU)

- Slit lamp examination:

	Right Eye	Left Eye
Lids/lashes	Normal	Normal
Conjunctiva/sclera	Normal	Normal
Cornea	Normal	Normal
Anterior Chamber	Deep & quiet	Deep & quiet
Iris	Single posterior synechia at 6 o'clock	Normal
Lens	Clear	Clear
Anterior Vitreous	Normal	Normal

Slit Lamp Exam

- Dilated Fundus Examination (DFE):

	Right Eye	**Left Eye**
Vitreous	Clear	Clear
Disc	Mild pallor	Slightly elevated, mild pallor, dragged temporarily

Cup-to-disc ratio	0.1	0.1
Macula, vessels, and periphery	Vessel dragging/straightening; diffuse pigmentary clumps in the periphery; subretinal exudation with inferior shallow detachment	Vessel dragging/straightening; diffuse pigmentary clumps in the periphery; less subretinal exudation than right eye concentrated peripherally; 360-degree peripheral anterior loop traction with fibrovascular proliferation, underlying vessels, and traction on peripheral retina

Dilated Fundus Examination (DFE)

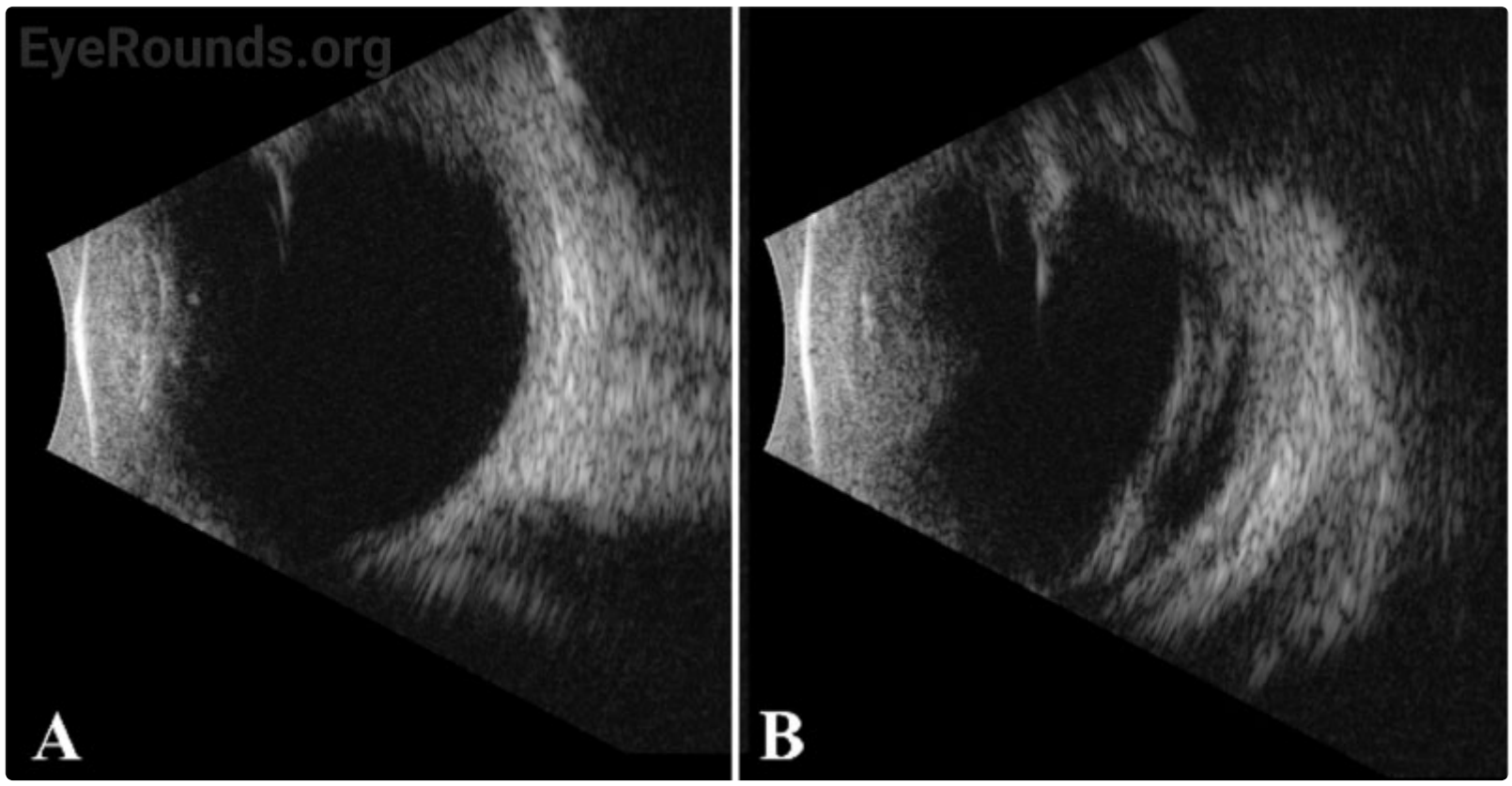

Figure 1. **B-scan echography, right (A) and left (B) eyes.** The right eye had a localized shallow inferior detachment, while the left eye had a hyperechoic membranous elevation inferiorly and temporally.

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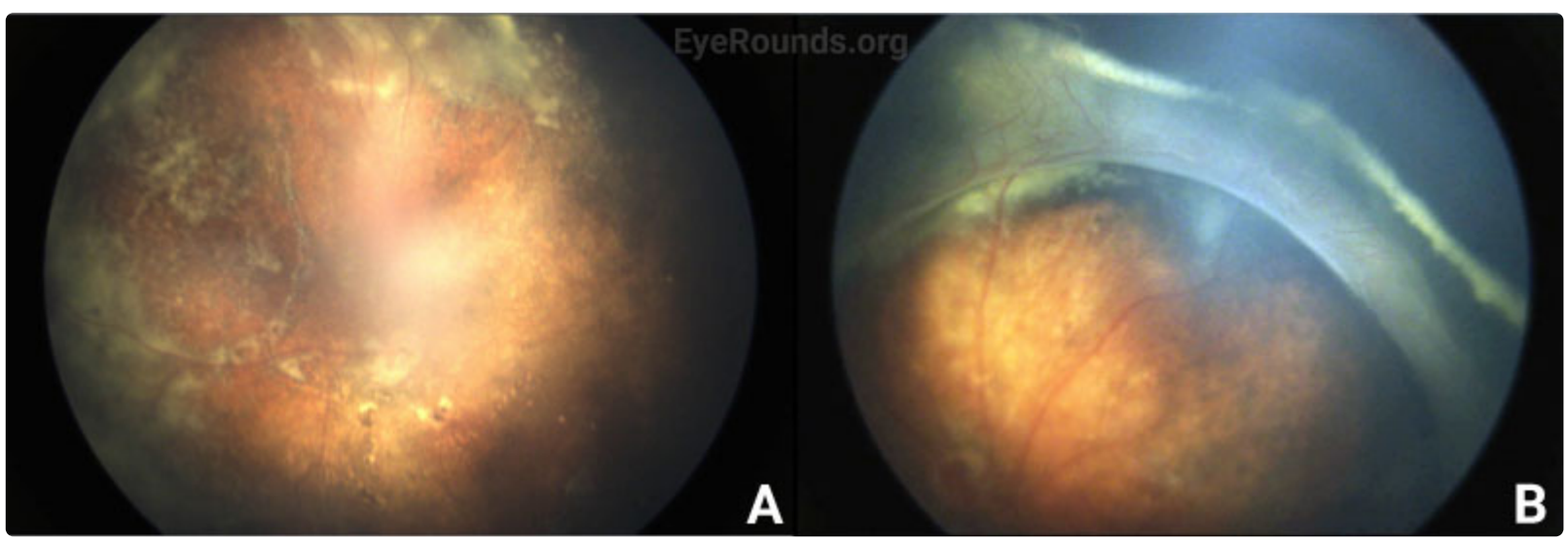

Figure 2. Fundus photographs, right (A) and left (B) eyes. Right eye fundus photo demonstrated a distorted macula with diffuse pigmentary clumping and subretinal exudates. Left eye fundus photo showed peripheral anterior loop traction with an opacified vitreous base and fibrovascular proliferation and exudates along this ridge.

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Differential Diagnosis:

- Retinopathy of prematurity
- Coats disease
- Norrie disease
- Persistent fetal vasculature
- Toxocara canis
- Incontinentia pigmenti

DIAGNOSIS: Familial Exudative Vitreoretinopathy (FEVR)

CLINICAL COURSE

The patient's exam findings on EUA were consistent with bilateral familial exudative vitreoretinopathy (FEVR), stage 3B.[1] Operative notes from the outside surgeon indicated that at the time of vitrectomy there was bilateral stage 4B disease. During the EUA, fluorescein angiography demonstrated peripheral neovascularization and ischemia 360 degrees extending to the posterior margin of zone 2 (Figure 3). Given the extensive bilateral neovascularization, panretinal photocoagulation (PRP) was applied to areas of ischemia, which extended from 2–3 disc diameters anterior to the macula up to the visualized fibrovascular ridge. Ablative laser was also applied to areas of shallow retinal detachment that were ischemic but without overlying fibrovascular membranes.

The patient returned one month later for post-operative evaluation. His mother reported increased responsiveness and tracking to bright light. Fundus exam showed extensive retinal scarring. The retinas were attached except for residual anterior loop traction with peripheral tractional detachment in the left eye. Six months later, the patient was tracking to light, and the retinas remained attached.

Genetic testing showed an LRP5 mutation (single copy variant of uncertain significance c.685C>T).

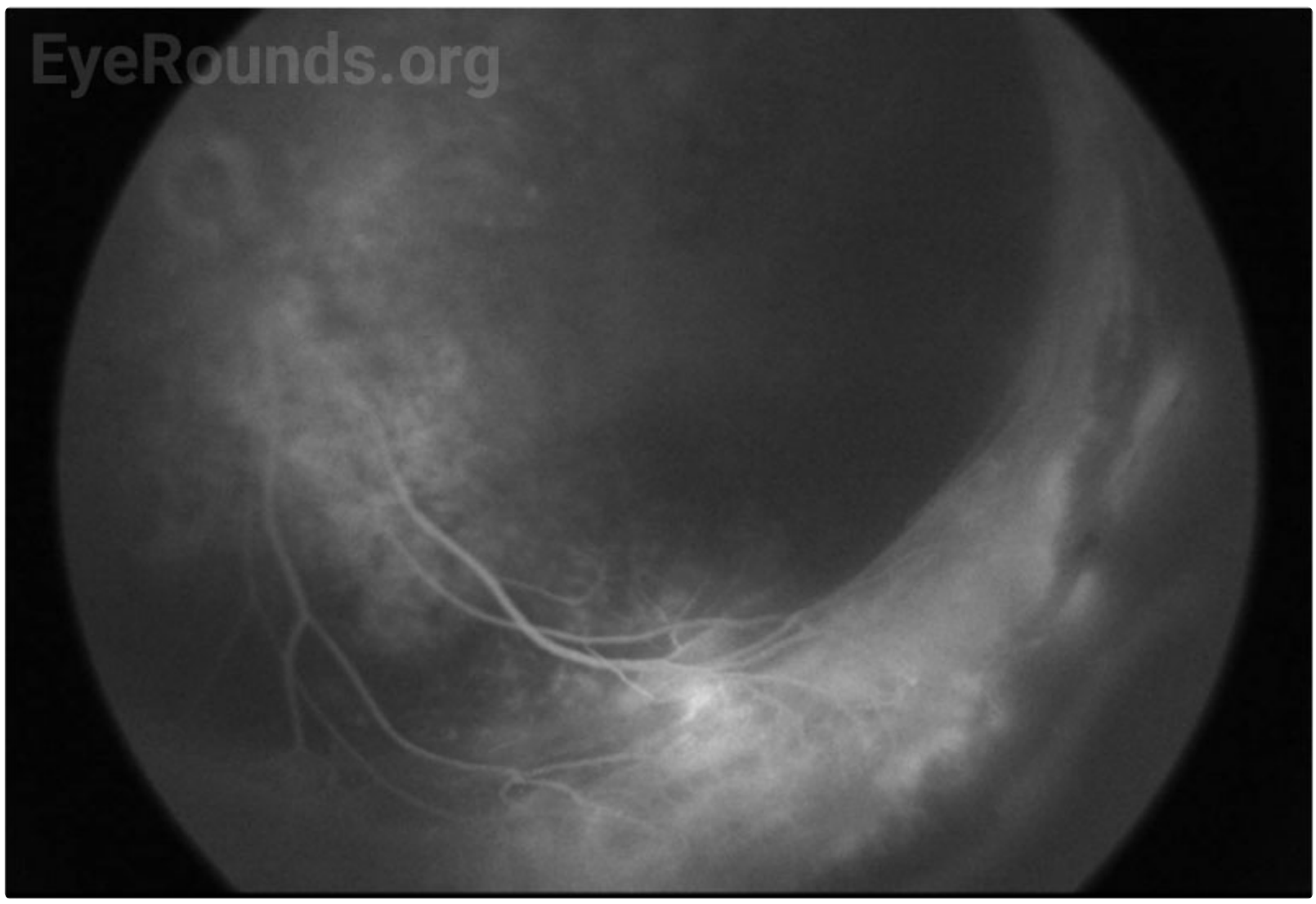

Figure 3. Fluorescein angiography, left eye demonstrating peripheral ischemia and neovascularization 360 degrees extending to posterior zone 2 with a peripheral ridge containing neovascular tufts.

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DISCUSSION

Etiology/Epidemiology

FEVR was first reported in 1969 by Criswick and Schepens, who described a progressive, inherited retinal vascular disease resembling retinopathy of prematurity (ROP) that occurred in patients without prematurity.[2]

Due to its rarity and heterogenous nature, the exact prevalence of FEVR is unknown. There is no gender predilection. Mutations in at least 10 genes (LRP5, FZD4, NDP, ZN408, KIF11, TSPAN12, CTNNB1, JAG1, DOCK6, and ARGHGAP31) have been associated with FEVR.[3-21] However, penetrance and expressivity are variable within families. Only 35-50% of patients with FEVR have a detectable mutation in one of these 10 known causative genes.[1]

Pathophysiology

FEVR results from mutations that disrupt signaling in the transduction pathways controlling retinal vascular development, cellular migration, and differentiation. Because of abnormal retinal angiogenesis, there can be exudative retinopathy and/or peripheral retinal ischemia, leading to neovascularization, retinal dragging, and tractional retinal detachment.

As mentioned above, FEVR is caused by mutations in multiple genes. The inheritance pattern can be autosomal dominant, autosomal recessive, or X-linked, though autosomal dominant is most common.[2,3] Most FEVR genes, including LRP5, FZD4, TSPAN12, and NDP, are involved in signal transduction within the WNT pathway, which regulates retinal vascular development.[2] Additional genes and pathways linked to FEVR are beyond the scope of this review.

Signs/Symptoms

FEVR presents with bilateral, abnormal retinal vasculogenesis in children without underlying risk factors for retinopathy of prematurity (i.e., full term, normal birth weight, no supplemental oxygen use). In children, FEVR can be diagnosed because of an abnormal newborn exam, behavioral changes, strabismus/amblyopia, or asymptomatic screening in families carrying a FEVR diagnosis. Between 10-50% of patients have a positive family history.[23] Some affected family members may be asymptomatic but have clear vascular abnormalities on fluorescein angiography.[1]

FEVR is a clinical diagnosis based on dilated fundus examination, often with supplemental fluorescein angiography. FEVR can feature some or all of the following: avascular peripheral retina (most often the temporal quadrant), dragged retinal vessels and macula (temporally), retinal falciform fold, neovascularization, vitreous hemorrhage, subretinal/intraretinal exudates (occasionally in massive quantities, resembling Coats disease), retinal detachment (which can be exudative, tractional, and/or rhegmatogenous; they occur in 21-64% of patients, and present bilaterally in 68%), persistent fetal vasculature, epiretinal membrane, and peripheral pigmentation (most prominent in the avascular retinal areas).[2,3] As a result of macular temporal dragging, patients may have pseudo-exotropia. Staging criteria for FEVR are shown in Table 1.

Stage	Description	Sub-stage	
		A	B
1	Avascular periphery and/or anomalous intraretinal vasculature	Without exudate	With exudate
2	Avascular periphery with preretinal neovascularization	Without exudate	With exudate
3	Extramacular retinal detachment	Without exudate	With exudate
4	Subtotal macula-involving retinal detachment	Without exudate	With exudate
5	Total retinal detachment	Open funnel	Closed funnel

Table 1. Staging criteria for FEVR

Not all cases of FEVR are symptomatic or progressive.[4] Some patients are not diagnosed with FEVR until adolescence, when the disease often progresses. Rarely, a patient is not diagnosed until adulthood, such as if they are screened because of a FEVR diagnosis in a symptomatic relative. The average age at diagnosis is 58.6 months.[3] Severity is often inversely proportional to age of diagnosis. FEVR rarely progresses in adulthood, although vitreous hemorrhage and other vision-threatening complications can occur.[5] Thus, long term follow-up is imperative.

Testing/Laboratory work-up

Testing/Laboratory work-up

In addition to a thorough dilated fundus exam, which may require EUA in children, wide-angle fluorescein angiography (FA) is helpful in diagnosing FEVR, especially in milder cases where only the far peripheral retina is affected. Typical findings on fluorescein angiography include a V-shaped avascular zone in the temporal periphery.[1] Peripheral avascularity can extend 360 degrees in more severe cases. Additional evidence on FA that suggests FEVR includes vessel straightening, peripheral telangiectasias, neovascularization, and small-vessel fluorescein leakage, as shown for a separate patient in Figure 4.[2]

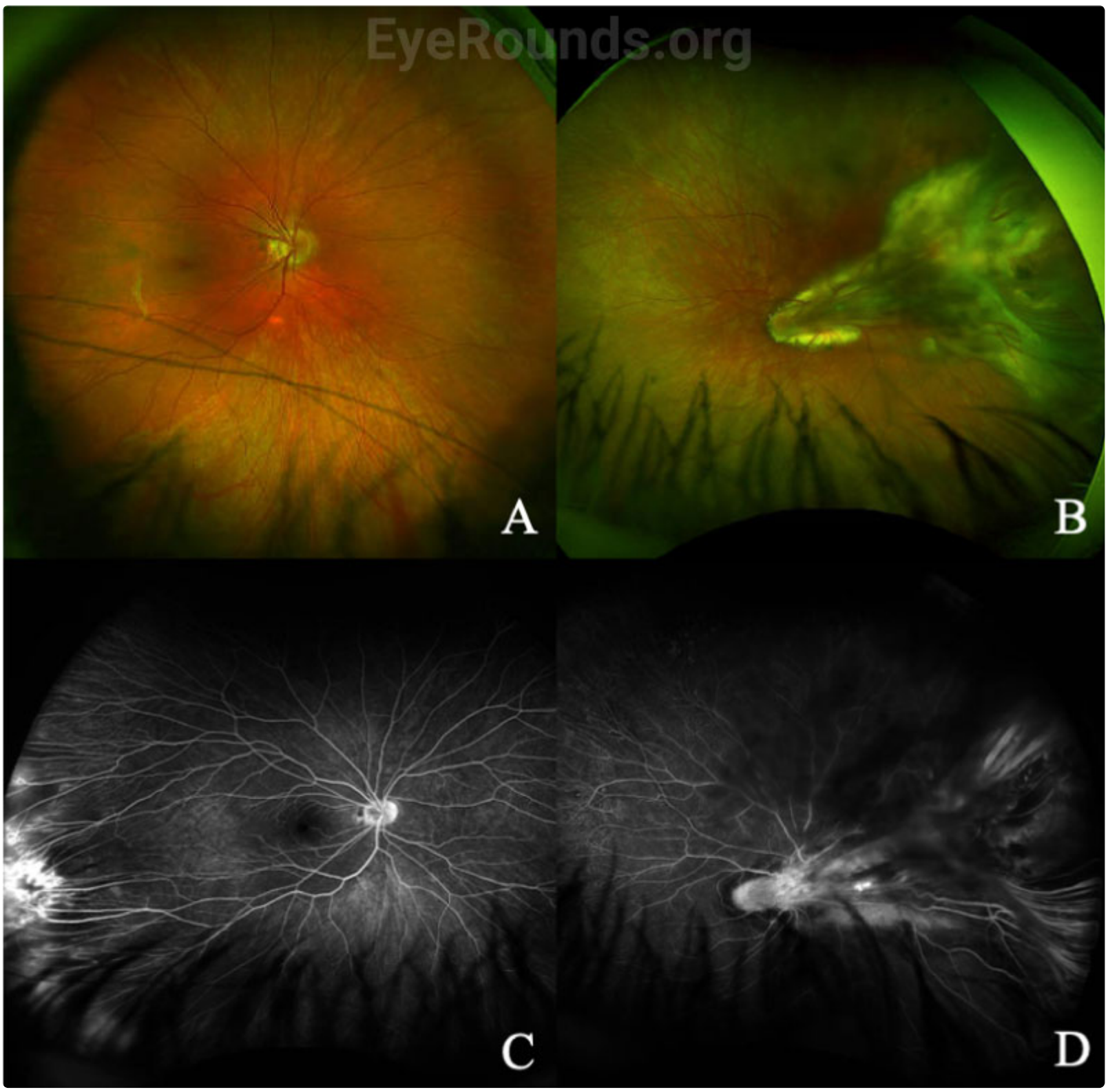

Figure 4. Fundus photography and fluorescein angiography of FEVR in an 18-year-old, right (A and C) and left (B and D) eyes. Although the fundus photo of the right eye shows only mild temporal vessel straightening, the FA shows peripheral non-perfusion, preretinal neovascularization, and vessel leakage. The left eye has a prominent falciform fold coursing from the optic nerve through the fovea to the temporal periphery, subretinal exudates, and vitreous bands overlying a tractional retinal detachment in the temporal periphery. The FA shows vessel straightening, peripheral nonperfusion with late, largely small-vessel leakage, staining in the area of exudation, and nasal PRP scars. This patient has stage 2A disease in the right eye and stage 4B disease in the left eye.

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Genetic testing is important to verify the diagnosis and to counsel patients and families. However, since fewer than 50% of FEVR cases can be attributed to a known gene, a negative genetic test result should not rule out a diagnosis of FEVR.[2]

Treatment/Management

The management of FEVR depends on the stage of disease. Stage 1 disease can be observed, while Stage 2 FEVR is usually treated with laser photocoagulation of avascular zones to decrease risk of exudation and neovascular complications such as vitreous hemorrhage and retinal detachment.[2] Compared to anti-VEGF agents, laser remains the mainstay of treatment, though anti-VEGF injections are sometimes used adjunctively, especially in the presurgical period to minimize intraoperative hemorrhage.[2,3] Treatment for stage 3-5 FEVR depends on the cause of retinal detachment. If exudative in nature, laser to avascular retina can be effective. Tractional and rhegmatogenous retinal detachments usually require retinal surgery; in infants, this is usually lens-sparing vitrectomy, whereas older children can often be treated with scleral buckling.

Genetic testing results inform screening of asymptomatic family members, a small percentage of whom may require treatment. Counseling female carriers of child-bearing age can facilitate pre-implantation genetic diagnosis and/or prompt screening of their newborns.

EPIDEMIOLOGY AND ETIOLOGY	DIAGNOSIS
◦ Abnormal retinal angiogenesis during early development ◦ Prevalence unknown ◦ 35-50% of patients carry mutations in LRP5, FZD4, NDP, ZN408, KIF11, TSPAN12, CTNNB1, JAG1, DOCK6, ARGHGAP31, ATOH7, or RCGTB1	◦ DFE/EUA ◦ Fluorescein angiography ◦ Genetic testing
SIGNS/SYMPTOMS	**TREATMENT/MANAGEMENT**
◦ Avascular peripheral retina in a full-term, normal weight infant without supplemental oxygen use ◦ Additional signs include retinal vessel straightening, macular dragging, subretinal exudates, preretinal neovascularization, retinal detachment, and pseudo-exotropia ◦ Preverbal status of many patients leads to diagnosis after abnormal newborn exam, change in behavior, or known family history	◦ Stage 1A and 1B: observation ◦ Stage 2: laser photocoagulation, and/or anti-VEGF ◦ Stage 3-5: laser, anti-VEGF, and/or retinal surgery

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