Familial Exudative Vitreoretinopathy

Results of Surgical Management

Scott D. Pendergast, MD, Michael T. Trese, MD

Objective: The purpose of the study was to report the results of surgical management of familial exudative vitreoretinopathy (FEVR).

Design: The study design was a retrospective clinical study.

Participants: A consecutive series of 52 eyes of 26 patients with FEVR were studied.

Intervention: All eyes underwent a complete ocular examination and were graded using a new classification system. Depending on the severity of disease, eyes were treated with peripheral laser photocoagulation, scleral buckling, or vitrectomy.

Main Outcome Measures: Preoperative and postoperative visual functions and anatomic status of the macula were the main parameters evaluated.

Results: A total of 40 eyes were treated. Seven eyes required no treatment and five eyes had inoperable retinal detachments. Fifteen eyes were treated with peripheral laser ablation initially and 25 eyes presenting with retinal detachments required vitreoretinal surgery. Of the 15 eyes treated initially with laser, 8 eyes required no further treatment, whereas 7 eyes progressed to retinal detachment requiring vitreoretinal surgery. A total of 32 eyes (including 7 previously lasered eyes) underwent vitreoretinal surgery. Twenty-nine of these 32 eyes had at least 6 months of follow-up. At the last follow-up visit, the macula was attached completely in 18 eyes (62.1%). Visual acuity ranged from 20/25 to light perception, with 10 (34.5%) of the 29 eyes achieving Snellen acuities of 20/100 or better. Two eyes (6.3%) progressed to no light perception.

Conclusion: These data suggest that surgical intervention can be beneficial in selected cases of FEVR.
Ophthalmology 1998;105:1015–1023

Familial exudative vitreoretinopathy (FEVR) is a vitreoretinal dystrophy characterized by premature arrest of vascularization of the peripheral retina. It is inherited as an autosomal-dominant[1–6] or X-linked recessive[7–9] trait with high penetrance and variable expressivity. Mild forms of the disease often are asymptomatic and show only peripheral vascular abnormalities such as a peripheral avascular zone, vitreoretinal adhesions, arteriovenous anastomoses, supernumerous vascular branching, and a V-shaped area of retinochoroidal degeneration. More severe manifestations include neovascularization, subretinal and intraretinal hemorrhage and exudates, and vascularized preretinal membranes that can lead to retinal folds, macula ectopia, and retinal detachment owing to vitreoretinal traction. Many of these findings are similar to those observed in retinopathy of prematurity (ROP), and therefore a careful history is necessary to distinguish these two disorders.[10] Unlike ROP, affected individuals with FEVR have a normal gestational period and lack a history of low birth weight and exposure to supplemental oxygen therapy. In addition, FEVR tends to be a variably progressive disorder, with detachments often not occurring until the first or second decade of life. When adulthood is reached, however, the retinal manifestations may appear to remain stable.[11,12]

Since FEVR was first described by Criswick and Schepens[13] in 1969, the funduscopic,[1–3,12,14] angiographic,[2,14,15] and histologic[16–18] features have been well documented. The current study presents a new classification system for FEVR and suggests a surgical management scheme for complications of FEVR in a pediatric population.

Originally received: October 4, 1996.
Revision accepted: November 25, 1997.

From the William Beaumont Eye Institute and Associated Retinal Consultants, P.C., Royal Oak, Michigan.

Presented in part at the Annual Meeting of the American Academy of Ophthalmology, Chicago, Illinois, October, 1996.

Supported in part by the Heed Ophthalmic Foundation (SDP).

Dr. Pendergast currently is affiliated with Retina Associates of Cleveland, Inc., Beachwood, Ohio.

Address correspondence to Michael T. Trese, MD, 632 William Beaumont Medical Building, 3535 W. Thirteen Mile Rd, Royal Oak, MI 48073.

Patients and Methods

Between January 1985 and February 1996, 40 eyes of 26 consecutive patients were managed surgically by one vitreoretinal surgeon for complications related to FEVR. A diagnosis of FEVR was established on the basis of the characteristic fundus findings and birth history. Whenever possible, the parents and siblings of the affected patient also were examined. Before surgery, all patients underwent a complete ophthalmologic evaluation, including visual acuity, ocular motility, anterior segment examination, and a dilated funduscopic examination. Examina-

Table 1. Clinical Classification of Familial Exudative Vitreoretinopathy

Stage	No. of Eyes* (n = 52)	Clinical Features
1	6	Avascular retinal periphery without extraretinal vascularization (n = 6)
2		Avascular reginal periphery with extraretinal vascularization
	0	Without exudate
	8	With exudate
3		Retinal detachment—subtotal, not involving fovea (n = 6)
	2	Primarily exudative
	4	Primarily tractional
4		Retinal detachment—subtotal, involving fovea (n = 18)
	4	Primarily exudative
	14	Primarily tractional
5		Retinal detachment—total (n = 14)
	7	Open funnel
	7	Closed funnel

* Eyes are classified based on clinical findings present at the time of initial presentation.

tion with the patient under anesthesia was performed when necessary.

Based on ophthalmoscopic findings, eyes were classified into one of the following five stages as summarized in Table 1. Stage 1 denotes the presence of a retinal avascular zone, typically involving the temporal periphery. The margin between vascular and avascular retina is characteristically thickened and may show a V-shaped notch at the horizontal temporal meridian. Stage 2 describes eyes with a peripheral avascular zone and extraretinal vascularization. Eyes were further subdivided into those without subretinal or intraretinal exudate (stage 2A) and those with exudate (stage 2B). Eyes with extensive exudate, arbitrarily defined as exudate extending greater than 4 disc diameters posterior to the peripheral avascular margin or fibrovascular membrane, were considered to be exudative detachments and were classified as stage 3A or 4A, as described below. Other findings, such as white without pressure, vitreous bands, retinochoroidal atrophy, hemorrhage, neovascularization, and dragging of the vessels, also may be present but were not specifically included in the classification.

Eyes showing findings described in stage 2 along with nonrhegmatogenous retinal detachments were grouped into stages 3, 4, and 5. Stage 3 includes eyes with partial retinal detachments not involving the fovea, whereas stage 4 denotes eyes with partial retinal detachments involving the fovea. In both stages 3 and 4, eyes were further subdivided into those detachments judged to be primarily effusive or exudative (stage 3A or 4A) and those judged to be primarily tractional (stage 3B or 4B), recognizing that in most cases, both components play a role. Detachments were presumed to be primarily tractional when the following findings were present: (1) vitreoretinal membranes or a fibrotic mass with attachments to the lens or anterior vitreous; (2) concavity of the retina; and (3) absence of extensive subretinal exudate or hemorrhage. The presence of significant vessel dragging and macular heterotopia also supports this designation. In contrast, retinal detachments were judged to be primarily effusive when significant amounts of subretinal fluid and exudate were present and the retinal configuration is typical of an exudative detachment with a more convex appearance. Finally, stage 5 includes eyes with total retinal detachments. Rather than subclassifying eyes based on the presumed underlying mechanism, eyes simply were subdivided into open-funnel (stage 5A) and closed-funnel (stage 5B) configurations.

In addition to the structural classification described above, other features of FEVR are important to consider. For example, the location and extent of vascularized retina can be characterized into zones 1, 2, and 3 using the same system devised for ROP staging.[6] The rate of progression of FEVR varies greatly from slowly progressive or nonprogressive to a rapidly progressive course, with stage 4 or 5 FEVR occurring at a young age. This classification scheme is designed to characterize the clinical appearance of eyes and is not intended to describe the tempo of progression.

Visual acuity testing was performed as follows. Best-corrected Snellen visual acuities were obtained after cycloplegic refraction and retinoscopy whenever possible. Both preoperative and postoperative cycloplegic refractions were performed by the referring ophthalmologists. In verbal patients with visual acuity less than 20/400, counting fingers, hand motion, light perception (LP), or no LP designations were used. In preliterate children, HOTV or illiterate E testing was used, whereas in infants, the ability to fix and follow was assessed. Preoperative visual-evoked potential testing was performed on preverbal children if there was uncertainty regarding the presence of visual function. In addition, on each visit, parents were questioned regarding the ability of the patient to function in various environments (e.g., ambulating, picking up small objects, looking at faces or bright objects, responding to light). Vision was arbitrarily defined as ''functional'' if it was sufficient for any of the following: ambulating without assistance, recognizing familiar faces or objects, or reading large print. These behavioral indicators are similar to those of the visual function battery reported by Droste and associates.[19] Grating acuity tests were not used in this study.

Treatment strategies fell into two general categories: (1) patients who presented initially with subretinal exudates or active extraretinal vascularization with no retinal detachment treated with peripheral laser ablation and (2) patients with retinal detachment or macula heterotopia who were treated with vitrectomy, scleral buckling, or both. However, some eyes with subtotal retinal detachment (stages 3 and 4) were treated initially with peripheral laser ablation in an attempt to induce regression of extraretinal vascularization and reduce the amount of subretinal exudate before vitrectomy. Some patients treated initially with laser progressed and eventually required vitrectomy. Laser ablation was conducted in the operating room with the patient under anesthesia with an indirect ophthalmoscope delivery system using either argon green (514 nm) or diode (810 nm) wavelengths. Laser burns of moderate intensity with a spot size of 500 μm spaced one half to one spot size apart were applied to the peripheral avascular retinal, sparing the vascular ridge.

Vitrectomy was performed using a two-port system with an infusion light pipe. Whenever possible, a lens-sparing approach was used as described previously.[20] In eyes in which the vitreoretinal membranes extended anteriorly and prevented safe entry through the pars plicata, entrance wounds were made at the limbus through the iris root and a lensectomy was performed. In nine cases, 0.4 unit of autologous plasmin enzyme was injected 15 minutes before surgery to facilitate membrane peeling in eyes with extensive preretinal membranes as part of an ongoing evaluation of enzymatic adjuncts to vitrectomy.[21] The goal of surgery was to relieve sufficient vitreoretinal traction so that the posterior pole could reattach.

The charts of all patients undergoing treatment for FEVR were reviewed retrospectively and the following information was recorded: age, age at time of initial intervention, family

Table 2. Patient Characteristics

Variable	N (%)
Sex (N = 26)	
Male	11 (42.3)
Female	15 (57.7)
Mean age (range)	6.1 ± 6.4 yrs (7 mos to 28 yrs)
Mean age at time of initial intervention (range)	3.2 ± 4.6 yrs (1 mos to 17 yrs)
Family history	
Yes	15 (57.7)
No	7 (26.9)
Unknown	4 (15.4)
Ocular involvement	
Bilateral	21 (80.8)
Unilateral	5 (19.2)
Baseline visual acuity (N = 52 eyes)	
20/20–20/100	5 (9.6)
20/125–20/400	3 (5.7)
CF–LP	39 (75.0)
NLP	5 (9.6)

CF = counting fingers; LP = light perception; NLP = no light perception.

history of FEVR, affected eye or eyes, dates of laser treatment or surgery, type of surgery performed, preoperative and final visual acuities, anatomic results, functional status, and follow-up period. In cases in which patients were referred from distant locations and could not return for subsequent follow-up examinations, information was obtained by contacting the referring ophthalmologist. For the purpose of statistical analysis, visual acuity data were entered into the database as decimal fractions such that 20/20 was entered as 1.0, 20/40 as 0.50, 20/80 as 0.25, 20/400 as 0.05, and so on. Both counting fingers and fix-and-follow vision were assumed to be equivalent to 0.5/200 and were assigned a value of 0.025, recognizing that in young children, the ability to fix and follow a target potentially could reflect much better visual function than the corresponding vision obtained in an adult. We believe this estimation is conservative in that it is possible to significantly underestimate visual function in some patients, whereas it is less likely that visual function would be overestimated because eyes with an ability to detect only hand motions or light would not be expected to maintain fixation. The numeric equivalents for hand motions, LP, and no LP were 0.0125, 0.00625, and 0.0, respectively. Mean and median visual acuities were calculated and are reported as Snellen equivalents.

Results

Patient Baseline Characteristics

A total of 26 patients diagnosed with FEVR were evaluated between January 1985 and February 1996. As summarized in Table 2, 11 patients (42.3%) were male and 15 (57.7%) were female. At the time of initial intervention with either laser or surgery, the mean age of the 26 patients was 3.2 ± 4.6 years (median, 1.25 years; range, 1 month–17 years). The mean age of the patients at the time of last follow-up examination was 6.1 ± 6.4 years (median, 4.5 years; range, 7 months–28 years). Twenty-one (80.8%) of the 26 patients had bilateral disease, and in 5 patients, disease was unilateral. A positive family history was identified in 15 cases (57.7%), a negative family history was confirmed by ocular examination in 7 cases (26.9%), and family members could not be examined in 4 cases. Forty eyes of 26 patients underwent treatment with peripheral laser ablation, surgical intervention, or both.

Preoperative visual acuities of the 40 treated eyes of 26 patients were measured despite the very young age of many of the patients. Only five eyes (12.5%) had Snellen visual acuities: 20/40 in one eye, 20/400 in three eyes, and 5/200 in one eye (Table 2). Three (7.5%) eyes could fix and follow a target or count fingers, and 4 (10%) eyes could detect hand motions, whereas the remaining 28 (70%) eyes could detect light or had a recordable visual-evoked potential. Baseline visual acuities of the 52 eyes in the series are summarized in Table 2.

We devised a new FEVR classification scheme, which is summarized in Table 1. The 52 eyes of 26 patients were grouped as follows based on the clinical findings at initial presentation. Six eyes showed only an avascular periphery and were classified as stage 1. No eyes showed stage 2A FEVR (extraretinal vasculature without exudate). Eight eyes had an avascular periphery with extraretinal vascularization and peripheral exudate (stage 2B). Six eyes had peripheral retinal detachments: two eyes were primarily exudative (stage 3A) and four eyes were primarily tractional (stage 3B). In 18 eyes, subtotal retinal detachments were observed involving the fovea and were therefore classified as stage 4: 4 cases in which the detachments were primarily exudative (stage 4A) and 14 cases in which the detachments were primarily tractional (stage 4B). Finally, 14 eyes had total retinal detachments (stage 5) on presentation, 7 eyes of which were at least partially open (stage 5A) and the remaining 7 eyes that were closed (stage 5B).

Laser Therapy

Fifteen eyes of 12 patients with a mean age of 4.4 ± 5 years (median, 3 years; range, 2 months–17 years) underwent peripheral laser ablation as initial therapy for FEVR (Table 3). The mean preoperative and final visual acuities for these 15 eyes were 20/400 (median, LP) and 20/150 (median, fix and follow), respectively (P = 0.007, Wilcoxon signed–rank test) after a mean follow-up of 30.4 months (range, 4–120 months). Final visual acuity was 20/100 or better in 4 (26.7%) of the 15 eyes, and 11 eyes (73.3%) were judged to show functional vision compared to 5 eyes (33.3%) before surgery (P = 0.23, Fisher's exact test). Of the five children who could not cooperate with Snellen visual acuity testing, five of these seven treated eyes could fix and follow and showed functional vision. Laser therapy required 1 session in 11 eyes (73.3%), 2 sessions in 3 eyes (20%), and 3 sessions in 1 eye (6.7%). In eight eyes, seven of which had at least 6 months of follow-up, the subretinal exudate resolved gradually, and no additional surgery has been necessary to date. Six of the eight eyes responding to laser alone were stage 2B, and two eyes were stage 4A. Only one of seven stage 2B eyes required further surgical intervention. Seven eyes ultimately required scleral buckling or vitrectomy surgery. The FEVR stages of these eyes were as follows: one eye, stage 2B; one eye, stage 3B; two eyes, stage 4A; and three eyes, stage 4B.

Surgical Intervention

Thirty-two eyes of 24 patients with FEVR underwent retinal detachment surgery (Table 4). The mean age at the time of initial vitreoretinal surgery was 3.3 ± 4.7 years (median, 1.25 years; range, 1 month–17 years). The breakdown of the 32 initial vitreoretinal surgical procedures was as follows: lens-sparing vitrectomy in 20 eyes (62.5%); lensectomy and vitrectomy in 6 eyes (18.8%); primary scleral buckling in 5 eyes

Table 3. Eyes Undergoing Peripheral Laser Ablation as Initial Therapy for FEVR

Patient No. (N = 12)	Age at Time of Initial Session	Family History of FEVR	Eye (N = 15)	FEVR Stage*	No. of Treatment Sessions	Subsequent Surgery Performed	Preoperative Visual Acuity	Final Visual Acuity	Follow-up (mos)
1	17 mos	Yes	OD	2B	2	No	LP	20/100	44
			OS	4A	1	Yes	LP	HM	44
2	3 mos	No	OD	2B	2	No	LP	F/F	44
			OS	4A	1	Yes	LP	NLP	44
3	3 mos	No	OD	2B	1	No	LP	F/F	12
7	2 mos	Yes	OD	2B	1	No	F/F	F/F	10
	2 mos		OS	2B	1	No	F/F	F/F	10
10	17 yrs	Yes	OD	4B	1	Yes	HM	LP	120
11	8 yrs	No	OD	2B	3	Yes	20/40	20/40	48
14	8 yrs	Yes	OS	4A	1	No	LP	20/20	15
15	3 yrs	No	OD	2B	1	No	LP	20/100	21
20	8 yrs	Yes	OD	4B	2	Yes	5/200	2/200	59
21	5 yrs	No	OD	4B	1	Yes	20/400	20/250	6
22	4 mos	No	OD	3B	1	Yes	LP	LP	21
25	7 mos	Yes	OS	4A	1	No	LP	F/F	4

F/F = fix and follow; HM = hand motion; LP = light perception; NLP = no light perception; FEVR = familial exudative vitreoretinopathy.
* Designates FEVR stage at time of initial presentation.

(15.6%); and scleral buckling and lens-sparing vitrectomy in 1 eye (3.1%). In addition, as part of a separate ongoing study, autologous plasmin was used as an adjunct in eight vitrectomy cases, seven of which were lens sparing. Of the 32 eyes undergoing surgery, 7 (21.9%) required a second procedure. Therefore, a total of 39 retinal surgery procedures (excluding laser) were performed on the 32 eyes.

Visual Acuity

The mean preoperative visual acuity for the 29 eyes undergoing vitreoretinal surgery with at least 6 months of follow-up was 20/800 (median = LP). The mean final visual acuity was 20/100 (median = fix and follow) after a mean follow-up of 38.3 ± 24.9 months ($P = 0.0001$, Wilcoxon signed–rank test). Of the 29 eyes undergoing surgery, final visual acuity improved in 16 eyes (55.2%), remained unchanged in 11 eyes (37.9%), and decreased in 2 eyes (6.9%). Sixteen eyes (55.2%) were judged to have functional vision on last examination compared to 5 eyes (17.2%) before surgery (phi = 0.411, $P = 0.048$, Fisher's exact test). However, many of the patients were preverbal at the time of surgery or laser, rendering assessment of visual acuity difficult. After the mean follow-up period of 35 months, visual acuities were obtained more easily, and this ascertainment bias should be considered when interpreting the results. The distribution of final visual acuities for the 36 treated eyes (7 eyes treated with laser alone and 29 eyes undergoing vitreoretinal surgery) with at least 6 months of follow-up is summarized in Table 5. Of the seven eyes treated with peripheral laser ablation alone, three eyes (42.9%) had final visual acuities of 20/100 or better and four eyes (57.1%) could fix and follow. Of the 29 eyes undergoing vitreoretinal surgery, final visual acuity was 20/100 or better in 10 eyes (34.5%) and fix and follow or better in an additional 6 eyes (20.7%). Final visual acuity was not associated with age at the time of initial intervention (rho = 0.116, $P = 0.58$, Spearman rank correlation). Not surprisingly, an inverse relationship was observed between the stage of FEVR at the time of initial laser or surgery and final visual acuity (rho = −0.411, $P = 0.017$, Spearman rank correlation).

Anatomic Results

Because of the inherent difficulties of determining visual acuity in a pediatric population, the anatomic status of the macula represents an important objective postoperative endpoint. Therefore, the anatomic status of the 36 eyes undergoing peripheral laser ablation or vitreoretinal surgery or both with at least 6 months of follow-up also was evaluated. As listed in Table 5, the macula was attached completely in each of the seven eyes treated with laser alone at the time of last examination. For the 29 eyes undergoing surgical intervention, the anatomic status of the macula was as follows: the macula was attached in 18 eyes (62.1%), partially attached in 7 eyes (24.1%), and remained detached in 4 eyes (13.8%). Perhaps not surprisingly, functional status was strongly associated with the anatomic status of the macula with functional vision observed more commonly in eyes in which the macula was fully attached when compared to eyes only partially attached or detached (chi-square = 21.8, $P < 0.0001$). Of the 18 eyes in which the macula was attached, 16 (88.9%) were judged to show functional vision, as defined in this study, whereas none of the eyes in which the macula was partially attached or detached showed functional vision. In 9 (50%) of the 18 eyes, visual acuity of 20/100 or better was achieved.

Progression of Disease

Although this study was not designed as a natural history study, several comments can be made regarding the progression of FEVR in the group of patients included in this study after a mean follow-up period of 35.2 months. Of the six stage 1 eyes, none showed progression of disease and no eyes in this group were treated. One stage 2B eye progressed to stage 3B 31 months after laser therapy and required lens-sparing vitrectomy. One stage 3B eye was treated with laser at the age of 4 months but progressed to stage 5B, requiring lensectomy and plasmin-assisted vitrectomy 8 months later. Two stage 4A eyes progressed to stage 4B. One eye of a 17-month old was treated with laser and required lens-sparing vitrectomy 5 months later. One eye of a 3-month old was treated with laser for stage 4A disease but required lensectomy and vitrectomy approximately

Table 4. Eyes Undergoing Surgery for FEVR

Patient No. (N = 24)	Age at Time of Initial Surgery	Family History of FEVR	Eye (N = 32)	FEVR Stage	Procedure	Preoperative Visual Acuity	Final Visual Acuity	Macula Status	Follow-up (mos)
1	2 yrs	Yes	OS	4B	1. LSVtx, ELP	LP			
					2. Drainage of subretinal blood 36 mos later	LP	HM	Attached	44
2	4 mos	No	OS	4B	Lensectomy, Vtx	LP	NLP	Detached	35
3	4 mos	No	OS	4B	Plasmin, LSVtx	LP	F/F	Partially attached	12
4	4 mos	Yes	OD	3B	LSVtx	LP	20/100	Attached	20
	4 mos		OS	3B	Lensectomy, Vtx	LP	20/100	Attached	20
5	3 yrs	Yes	OS	5A	Plasmin, LSVtx	LP	F/F	Attached	6
6	4 yrs	Yes	OS	5A	Plasmin, LSVtx	LP	LP	Partially attached	6
8	4 mos	Yes	OD	4B	LSVtx	LP	LP	Partially attached	39
9	7 mos	No	OD	4B	LSVtx	LP	20/50	Attached	69
	3 mos		OS	4B	LSVtx, ELP	LP	20/50	Attached	73
10	17 yrs	Yes	OD	4B	Scleral buckle	HM	LP	Detached	120
11	10 yrs	No	OD	3B	Plasmin, LSVtx	20/40	20/40	Attached	13
	7 yrs		OS	4B	LSVtx	20/400	20/25	Attached	48
12	5 mos	Unknown	OD	4B	LSVtx	LP	LP	Partially attached	2
13	1 yr	Yes	OD	4B	Lensectomy, Vtx	LP	20/40	Attached	27
	3 mos		OS	4B	1. LSVtx, ELP	Not measured	LP	Detached	35
					2. Lensectomy, Vtx, 8 mos later	LP			
14	3 yrs	Yes	OD	4B	LSVtx, ELP	LP	LP	Partially attached	60
16	1 yr	Yes	OS	4B	LSVtx	LP	CF	Attached	45
17	17 yrs	Yes	OS	5A	1. LSVtx, ELP, F/G	CF			
					2. Lensectomy, Vtx, 9 mos later	LP	LP	Detached	36
18	4 yrs	Unknown	OD	4B	1. LSVtx	LP			
					2. Lensectomy, Vtx, 16 mos later	LP	LP	Partially attached	42
19	2 yrs	Unknown	OD	3A	SB	F/F	20/30	Attached	52
	2 yrs		OS	3A	SB	F/F	20/160	Attached	52
20	8 yrs	Yes	OD	4B	SB, Cryopexy, LSVtx	5/200	2/200	Attached	56
	8 yrs		OS	3B	1. SB, Cryopexy	20/400	20/50	Attached	60
					2. LSVtx 1 mo later	8/200			
21	5 yrs	No	OD	4B	Plasmin, LSVtx, ELP	20/400	20/70	Attached	14
22	1 yr	No	OD	5B	Plasmin, lensectomy, Vtx	LP	Follows light	Partially attached	13
	2 mos		OS	5B	LSVtx	LP	HM	Partially attached	14
23	1 yr	Yes	OS	5A	1. Lensectomy, Vtx	LP			
					2. Plasmin, Vtx 14 mos later	LP	Follows light	Partially attached	15
24	8 mos	Unknown	OD	5A	Lensectomy, Vtx	LP	F/F	Attached	15
			OS	2B	1. SB, laser	LP			16
					2. Division of SB 6 mos later	F/F	HM	Attached	
25	7 mos	Yes	OD	5A	Plasmin, LSVtx	LP	F/F	Attached	4
26	3 mos	No	OS	5A	Plasmin, LSVtx	LP	F/F	Attached	4

FEVR = familial exudative vitreoretinopathy; LSVtx = lens-sparing vitrectomy; Vtx = vitrectomy; ELP = endolaser photocoagulation; LP = light perception; HM = hand motion.

1 month later for stage 4B FEVR. At 1 year of age, the disease progressed to stage 5B and vision deteriorated to no LP.

Discussion

Familial exudative vitreoretinopathy is an inherited retinal vascular disease with two well-documented modes of inheritance.[1-9] The clinical course of FEVR can vary greatly from nonprogressive or slowly progressive over a patient's lifetime to rapidly progressive with total retinal detachment occurring at a young age. Although FEVR is an uncommon entity, it represents a significant cause of retinal detachment in patients younger than 30 years of age.[14]

Previous classification schemes have grouped patients into three stages.[1,15] Stage 1 consisted of white with or without pressure, cystoid degeneration, vitreous bands, and vitreoretinal traction peripherally. Stage 2 was characterized by the changes mentioned above along with neovascularization in the temporal periphery associated with subretinal exudates and traction resulting in dragging of the disc and major retinal vessels. Stage 3 represented end-stage disease, namely, total retinal detachment with or without massive subretinal exudates, cataract, iris

Table 5. Final Results of Eyes Undergoing Treatment for FEVR with at Least 6 Months of Follow-up

Variable	Eyes Treated with Laser Only (n = 7) [no. (%)]	Eyes Undergoing Surgery (n = 29) [no. (%)]	Total (n = 36) [no. (%)]
Visual acuity			
20/20–20/100	3 (42.9)	10 (34.5)	13 (36.1)
20/125–20/400	0	1 (3.4)	1 (2.8)
2/200	0	1 (3.4)	1 (2.8)
F/F	4 (57.1)	4 (13.8)	8 (22.2)
CF	0	1 (3.4)	1 (2.8)
HM	0	4 (13.8)	4 (11.1)
LP	0	6 (20.7)	6 (16.7)
NLP	0	2 (6.9)	2 (5.6)
Macula status	7 (100)		
Attached		18 (62.1)	25 (69.4)
Partially attached	0	7 (24.1)	7 (19.4)
Detached	0	4 (13.8)	4 (11.1)
Mean follow-up (mos)	22.3 ± 15.3	38.3 ± 24.9	35.2 ± 24.0

F/F = fix and follow; CF = counting fingers; HM = hand motion; LP = light perception; NLP = no light perception; FEVR = familial exudative vitreoretinopathy.

atrophy, neovascular glaucoma, and band keratopathy. Nishimura et al[3] recommended the addition of stage 4 to include falciform retinal fold. More recently, Miyakubo et al[14] established a grading system consisting of five categories of FEVR based on the presence and intensity of the following vascular findings: retinal avascular zone in the farthest periphery or in a v-shaped pattern temporally, arteriovenous shunt formation, and retinal neovascularization.

We have devised a grading scheme that groups patients into five stages, bearing some resemblance to the well-established classification system used for ROP.[22] Unlike previous classification systems that emphasize less-severe manifestations of disease and group retinal detachments into a single stage, we divided eyes into groups according to severity of disease and type and extent of retinal detachment and further divided nonrhegmatogenous detachments into those with a predominantly effusive (exudative) component and those predominantly tractional.

Potential advantages of such a classification system include the following:

1. It conveys detailed information regarding the severity of FEVR and foveal involvement in cases of retinal detachment and therefore has prognostic implications.
2. The presumed underlying mechanism of retinal detachment is described, thereby guiding therapeutic decisions.
3. It facilitates mutual understanding among communicating ophthalmologists.

The distribution of eyes assigned to the various stages of our classification scheme is not representative of a typical FEVR patient population because patients were referred for consideration of laser or retinal surgery and therefore tended to have more severe manifestations. The majority of patients with FEVR have only mild disease and would be classified as stage 1 or 2, with various forms of retinal detachment occurring in approximately 20% of eyes studied in two large series.[12,14]

There are a paucity of studies evaluating the results of surgical intervention in eyes with subretinal exudate or retinal detachment related to FEVR. Early studies involving a small number of eyes advocated peripheral cryotherapy to ablate hyperpermeable vessels associated with the peripheral fibrovascular tissue to prevent progression of FEVR.[1,15] More recent studies have reported results of surgical management of retinal detachment associated with FEVR.[18,23]

The largest surgical series published to date was by van Nouhuys[12] in 1991. A total of 22 retinal procedures were performed by various surgeons and involved primarily scleral buckling alone or vitrectomy with or without scleral buckling. Surgery was performed on 14 eyes of 14 patients with retinal detachments related to FEVR. The results were somewhat discouraging, with reattachment of the retina occurring in seven eyes after one or more operations. In 5 cases, the retina was reattached with scleral buckling alone, whereas only 2 of 12 vitrectomies were successful. Interestingly, all seven of these eyes were in adults with ages ranging from 19 to 56 years. In the group of patients whose retinas failed to reattach, ages ranged from 5 to 18 years with a mean age of 13 years. The current series may not be comparable to the results in the above series owing the differences in the distribution of ages and the high proportion of rhegmatogenous detachments included in van Nouhuy's series. The current study is skewed toward younger patients with retinal complications of FEVR (mean age at time of initial intervention, 3.2 years) owing to the referral patterns of one of the authors (MTT).

In discussing the surgical outcomes of the patients presented in this series, it is useful to consider the therapeutic approaches and outcomes in the context of the stage of disease. As discussed above, eyes were divided into one of five stages based on the severity of diseases and the

Table 6. Results of Initial Management of FEVR Classified by Stage

			Eyes Undergoing Surgery‡					Macula Status§			
FEVR Stage*	**Initial Laser†**	**Subsequent Surgery**	*LSVTX*	*LVTX*	*Plasmin*	*SB*	*Further Surgery*	*Attached*	*Partially Attached*	*Detached*	**Median Final VA‖**
1	0/6	—	—	—	—	—	—	6/6	0/6	0/6	20/20
2B	7/8	1/7¶	0/1	0/1	0/1	1/1	1/1	7/7	0/7	0/7	F/F
3A	0/2	—	0/2	0/2	0/2	2/2	0/2	2/2	0/2	0/2	20/30 20/160
3B	1/4	1/1**	2/4	1/4	1/4	1/4	1/4	4/4	0/4	0/4	20/100
4A	4/4	2/4††	—	—	—	—	—	2/2	0/2	0/2	20/20 F/F
4B	3/14	3/3	13/16	2/16	2/16	2/16‡‡	3/16	8/16	5/16	3/16	F/F
5A	0/7	—	5/7	2/7	4/7	0/7	2/7	4/7	2/7	1/7	F/F
5B	0/7	—	1/2	1/2	1/2	0/2	0/2	0/2	2/2	0/2	HM, LP FL
Total	15/52	7/15	21/32	6/32	8/32	6/32	7/32	27/40	9/40	4/40	

LSVTX = lens-sparing vitrectomy; LVTX = lensectomy and vitrectomy; SB = scleral buckle; VA = visual acuity; F/F = fix and follow; HM = hand motions; LP = light perception; FL = follows light; FEVR = familial exudative vitreoretinopathy.

* Indicates the stage of FEVR either at the time of initial presentation (for columns Initial Laser and Subsequent Surgery) or the stage observed at the time of initial surgery (for eyes listed under Eyes Undergoing Surgery).

† The numerator denotes the number of eyes of a given stage undergoing laser as initial treatment of FEVR and the denominator represents the total number of eyes in the group.

‡ The numerator indicates the number of eyes undergoing the surgical procedure listed and the denominator represents the total number of eyes undergoing surgery for each FEVR stage.

§ The six eyes with stage 1 FEVR are not included in the total.

‖ In groups containing less than four eyes, individual visual acuities listed.

¶ One eye progressed to stage 3B at the time of surgery.

** One eye progressed to stage 5B at the time of surgery.

†† Two eyes progressed to stage 4B at the time of surgery.

‡‡ Scleral buckling surgery performed at time of initial vitrectomy for one eye.

extent of retinal detachment. Although this grading system is somewhat broad and emphasizes more severe forms of FEVR, it is useful in that eyes assigned to a given stage tend to share both clinical and presumed pathophysiologic features and therefore would be expected to respond to similar treatment strategies. However, this classification scheme is designed to characterize the clinical appearance of eyes and does not describe the tempo of progression. A summary of the results of surgical management of FEVR based on the stage of disease is listed in Table 6 and is discussed below.

Eyes showing only peripheral avascularity (stage 1) were not treated. None of the six eyes progressed to a more advanced stage over a mean follow-up of 33 months (median, 13.5 months). Eyes with significant subretinal or intraretinal exudate from vascular hyperpermeability (stage 2B) achieved excellent results from peripheral laser ablation alone. Of the seven stage 2B eyes treated initially with laser, six eyes showed improvement or preservation of visual function, a decrease in the amount of exudate, and showed no evidence of progression after a mean follow-up of 23.5 months (range, 10–44 months). One eye progressed to stage 3B FEVR with fibrovascular membranes involving the lens and was treated successfully with injection of autologous plasmin and lens-sparing vitrectomy.

Eyes with retinal detachment were treated somewhat differently depending on the predominant mechanism at work. In partial retinal detachments with a predominately effusive or exudative component (stage 3A or 4A), scleral buckling with or after laser appears to be the most appropriate initial therapy. Of the two stage 3A eyes observed in one patient, both were treated successfully with scleral buckling alone. The four stage 4A eyes were all treated initially with laser. In two cases, the exudate resorbed with improvement in visual acuity from LP to 20/20 and fix and follow, respectively, and no further intervention was necessary. In the remaining two cases, subsequent vitreous surgery was required.

Partial retinal detachment owing primarily to traction was the most commonly encountered clinical situation in this series with 4 stage 3B eyes and 16 stage 4B eyes. Because these stages differ only in the extent of retinal detachment (involvement of the macula), eyes with stage 3B and 4B FEVR were managed similarly. Of the four stage 3B eyes, extensive traction was exerted by anterior fibrovascular proliferation involving the lens in three eyes. In one eye, lensectomy and vitrectomy were necessary to relieve the traction. In two eyes, lens-sparing vitrectomy was performed and in one of these cases (patient 11), plasmin facilitated nontraumatic removal of membranes from the posterior lens capsule of the right eye. Primary scleral buckling and cryotherapy were performed in one eye without success, and a lens-sparing vitrectomy subsequently was performed. The macula remained attached in each case with visual acuities of 20/100 or better.

Of the 14 eyes presenting with stage 4B FEVR, 3 eyes were treated initially with peripheral laser ablation, and in each case, subsequent surgery was required. Of the 16 stage 4B eyes undergoing surgery, 13 eyes underwent lens-sparing vitrectomy, 2 eyes required lensectomy and vitrectomy, and 1 eye was managed by scleral buckling alone. The anatomic and visual acuity outcomes for eyes with stage 4B FEVR were encouraging, although results were somewhat less promising than observed in stage 3B eyes. The median final visual acuity was fix and follow with five eyes (31.3%) showing visual acuities of 20/70 or better. The macula was attached completely in 8 of the 16 eyes, partially attached in 5 eyes, and remained detached in 3 eyes. Additional surgery was required in 3 of 13 eyes managed initially with lens-sparing vitrectomy.

Eyes with total retinal detachments in an open-funnel configuration (stage 5A) were managed similarly to stage 4B eyes and appeared to respond equally well. Of the seven stage 5A eyes with a total retinal detachment in an open-funnel configuration, five were managed initially with lens-sparing vitrectomy, whereas two eyes required lensectomy. Final visual acuities were fix and follow in four eyes and LP in the remaining three eyes. The macula was attached in four eyes, was partially attached in two eyes, and remained detached in one eye despite subsequent lensectomy and vitrectomy. Of the four eyes managed initially with plasmin and lens-sparing vitrectomy, the macula was attached in three eyes and partially attached in one eye.

As expected, eyes with total retinal detachment in a closed-funnel configuration (stage 5B) carry a more guarded prognosis. Of the seven stage 5B eyes, five eyes displayed no evidence of visual function on examination or on visual-evoked potential testing and were not surgical candidates. Two eyes of one patient underwent vitrectomy for stage 5B FEVR. Patient 22 presented with stage 3B FEVR in the right eye and stage 5B in the left eye. The left eye underwent lens-sparing vitrectomy at the age of 2 months, resulting in partial attachment of the posterior pole with hand motions visual acuity after 14 months of follow-up. The right eye was managed initially with laser but progressed to stage 5B and subsequently underwent injection of plasmin, lensectomy, and vitrectomy. Partial attachment of the posterior pole was achieved with the ability to follow a light source after 13 months of follow-up.

In summary, although studies documenting the natural history of FEVR are not available, it is thought that FEVR represents a progressive life-long disease, and variable tempos appear to exist. Based on these features and the results of this study, we recommend the following:

1. Eyes with stage 1 FEVR required no therapy and should be observed.
2. Eyes with earlier stages of FEVR without retinal detachment (stage 2B) achieved excellent results after laser ablation alone.
3. Eyes with retinal detachments generally required scleral buckling or vitrectomy depending on the extent of the detachment and the location and degree of vitreoretinal traction. Stage 3A eyes responded favorably to scleral buckling alone, whereas all stage 3B, 4B, and 5 eyes ultimately required vitrectomy.
4. Because anatomic and visual function results were less promising in eyes with more advanced stages of FEVR, early intervention appears beneficial. Affected patients should be examined regularly over their lifetime, and family members should be screened to detect FEVR at an early stage.

References

1. Gow J, Oliver GL. Familial exudative vitreoretinopathy. An expanded view. Arch Ophthalmol 1971;86:150–5.
2. Miyakubo H, Inohara N, Hashimoto K. Retinal involvement in familial exudative vitreoretinopathy. Ophthalmologica, Basel 1982;185:125–35.
3. Nishimura M, Yamana T, Sugino M, et al. Falciform retinal fold as sign of familial exudative vitreoretinopathy. Jpn J Ophthalmol 1983;27:40–53.
4. Nicholson DH, Galvis V. Criswick–Schepens syndrome (familial exudative vitreoretinopathy). Study of a Colombian kindred. Arch Ophthalmol 1984;102:1519–22.
5. Li Y, Fuhrmann C, Schwinger E, et al. The gene for autosomal dominant familial exudative vitreoretinopathy (Criswick–Schepens) on the long arm of chromosome 11. Am J Ophthalmol 1992;113:712–3.
6. Li Y, Muller B, Fuhrmann C, et al. The autosomal dominant familial exudative vitreoretinopathy locus maps on 11q and is closely linked to DIIS533. Am J Hum Genet 1992;51:749–54.
7. Plager DA, Orgel IK, Ellis FD, et al. X-linked recessive familial exudative vitreoretinopathy. Am J Ophthalmol 1992;114:145–8.
8. Shastry BS, Trese MT. X-linked familial exudative vitreoretinopathy. Am J Med Genet 1993;45:111–3.
9. Clement F, Beckford CA, Corral A, Jimenez R. X-linked familial exudative vitreoretinopathy. Report of one family. Retina 1995;15:141–5.
10. Campo RV. Similarity of familial exudative vitreoretinopathy and retinopathy of prematurity. Arch Ophthalmol 1983;101:821.
11. Ober RR, Bird AC, Hamilton AM, Sehmi K. Autosomal dominant exudative vitreoretinopathy. Br J Ophthalmol 1980;64:112–20.
12. van Nouhuys CE. Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy. Am J Ophthalmol 1991;111:34–41.
13. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. Am J Ophthalmol 1969;68:578–94.
14. Miyakubo H, Hashimoto K, Miyakubo S. Retinal vascular pattern in familial exudative vitreoretinopathy. Ophthalmology 1984;91:1524–30.
15. Canny CLB, Oliver GL. Flourescein angiographic findings in familial exudative vitreoretinopathy. Arch Ophthalmol 1976;94:1114–20.
16. Brockhurst RJ, Albert DM, Zakov ZN. Pathologic findings in familial exudative vitreoretinopathy. Arch Ophthalmol 1981;99:2143–6.
17. Boldrey EE, Egbert P, Gass JDM, Friberg T. The histopathology of familial exudative vitreoretinopathy. A report of two cases. Arch Ophthalmol 1985;103:238–41.
18. Glazer LC, Maguire A, Blumenkranz MS, Trese MT, Green WR. Improved surgical treatment of familial exudative vitreoretinopathy in children. Am J Ophthalmol 1995;120:471–9.

19. Droste PJ, Archer SM, Helveston EM. Measurement of low vision in children and infants. Ophthalmology 1991; 98:1513–8.
20. Maguire AM, Trese MT. Lens-sparing vitreoretinal surgery in infants. Arch Ophthalmol 1992;110: 284–6.
21. Verstraeten TC, Chapman C, Hartzer M, et al. Pharmacologic induction of posterior vitreous detachment in the rabbit. Arch Ophthalmol 1993;111:849–54.
22. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol 1984;102:1130–4.
23. Bergen RL, Glassman R. Familial exudative vitreoretinopathy. Ann Ophthalmol 1983;15:275–6.

Discussion by William Tasman, MD

Drs. Pendergast and Trese present a comprehensive experience in the surgical management of dominant familial exudative vitreoretinopathy (FEVR). Their study revealed an almost equal number of males and females. A positive family history was documented in 15 cases and a negative family history in 7 cases. With regard to those with a negative family history, it is interesting to speculate on whether some of these cases might represent Norrie's disease, because both X-linked FEVR and Norrie's disease have demonstrated a defect at the Xp11 locus.[1] Chen has described a pedigree of X-linked FEVR with a mutation in the Norrie's disease gene.[2] The evidence supports the argument that Norrie's and X-linked FEVR are allelic.

Drs. Pendergast and Trese also propose a classification for FEVR. Because retinopathy of prematurity (ROP) and FEVR often may have similar clinical presentations, their classification, understandably, in some ways parallels that of ROP. For example in stage 3 of the authors' classification, retinal detachment may be subtotal in which case it does not involve the fovea, whereas in stage 4, the fovea is involved. In ROP, stage 4A represents subtotal retinal detachment with macular sparing and stage 4B involves the fovea. Both stage 3 and stage 4 of the FEVR classification have subcategories of "primarily exudative" and "primarily tractional" that, in my experience, are sometimes difficult to differentiate. The exudation usually is secondary to abnormal vasculature in the far retinal periphery, but in our experience, this may be coupled with vitreous or membranous traction on the vessels.

As the authors indicate, to eliminate exudation, one must first eliminate the abnormal vasculature. Toward that end, Drs. Pendergast and Trese were able to initially treat 15 eyes with laser only, 8 of which did not require further treatment. An additional 32 eyes underwent vitreoretinal surgery.

The authors' experience parallels our own. Knowing which eyes to treat, of course, is always difficult. As the authors mentioned, there is no good natural history study. In a thesis by Benson,[3] he looked at the natural history with emphasis on the effect of the age of onset, the severity of the disease, and the development of late complications such as cataract and retinal detachment. Only 2 of 28 patients in that study whose onset of symptoms was before their third birthday had a final visual acuity of 20/200 or better. It appeared that older patients had a better prognosis because they were more likely to have asymmetric retinal involvement with only one eye severely affected. However, preservation of good vision into the teens and beyond was no guarantee that deterioration would not occur. This is a point made by the authors and one with which we agree. Clearly, FEVR is a lifetime disease.

In our experience, we have seen patients in their late twenties develop vitreous hemorrhaging and retinal detachment that required surgical intervention. On follow-up of seven patients (8 eyes) with tractional or rhegmatogenous retinal detachment or both for 2 to 9 years with an average of 7 years, retinal reattachment was achieved in six of the eight eyes with vitreoretinal surgery. In many instances, however, the vision was not good, although it was functional, because of dragging of the retina. Many of the eyes reported in the series by Drs. Pendergast and Trese had similar outcomes.

As the authors point out, those that would appear to have the best prognosis are the ones with early exudation in which the abnormal vessels can be lasered or treated with cryotherapy.

From Wills Eye Hospital, 900 Walnut Street, Philadelphia, PA 19107.

References

1. Fullwood P, Jones J, Bundey, S, et al. X linked exudative vitreoretinopathy: clinical features and genetic linkage analysis. Br J Ophthalmol 1993;77:168–70.
2. Chen ZY, Battinelli EM, Fielder A, et al. A mutation in the Norrie disease gene (NDP) associated with X-linked familial exudative vitreoretinopathy. Nat Genet 1993;5: 180–3.
3. Benson WE. Familial exudative vitreoretinopathy. Trans Am Ophthalmol Soc 1995;93:473–521.