Persistence of the Fetal Vasculature: Varieties and Management

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Abstract

The spectrum of persistence of the fetal vasculature (PFV) is broad and includes anterior segment as well as vitreal and retinal abnormalities. The great majority of cases are unilateral and not associated with other systemic abnormalities. Some patients can be observed and the ocular abnormalities are inconsequential; others require surgical interventions such as lens extraction, anterior vitrectomy, and occasionally posterior vitreoretinal maneuvers. Rarely, patients have very small eyes with disorganized vitreous and a very poor visual outcome; in such cases, the lens is often removed to avoid angle closure glaucoma and phthisis bulbi. Accurate diagnosis and appropriate management are associated with acceptable outcomes in a majority of cases.

Keywords

Persistent fetal vasculature • Persistent hyperplastic primary vitreous • Pupillary membrane • Embryology • Cataract • Cloquet canal • Malformation

Introduction

Persistence of the fetal vasculature (PFV) refers to a spectrum of ocular abnormalities characterized by deformations and malformations of ocular structures that result from failure of some of the ophthalmic fetal vasculature to regress and form an accompanying fibrotic response. Abnormalities of regression of fetal vasculature in any location in the eye, especially in the anterior vitreous and around the iris, result in the clinical spectrum of PFV, which includes what was previously referred to as persistent hyperplastic primary vitreous (PHPV), persistent tunica vasculosa lentis, as well as other discrete ocular findings, such as inconsequential remnants of the pupillary membrane, and Mittendorf dot on the back of the lens. In 1997, Goldberg proposed integrating the numerous clinical variations of failed regression of the embryonic vasculature involving the anterior and posterior segment under the umbrella term of PFV [1]. The etiology of PFV remains unclear but factors that interfere with regression and absorption of fetal structures and blood vessels are evidently at play. These factors probably include genetic and environmental components.

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Clinical Presentation

Signs

The presentation of patients depends on the severity of the variety of PFV. In those with iris and pupillary abnormalities (Fig. 20.1), the diagnosis may be made shortly after birth because of the flagrant appearance of the anterior segment. Those with a small eye and severe anterior and posterior

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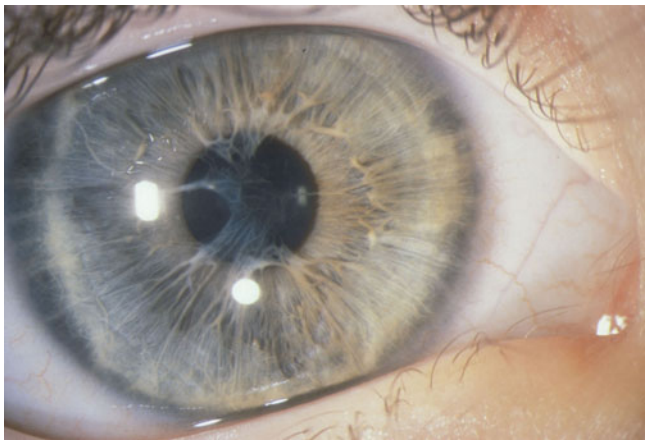

Fig. 20.1 Remnants of the pupillary membrane. Some attach to the anterior lens capsule

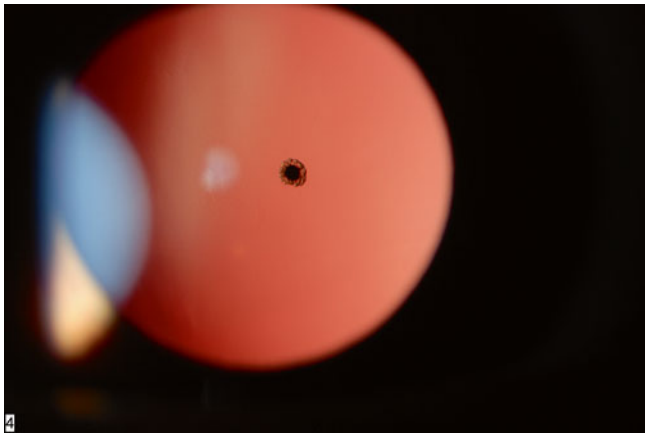

Fig. 20.2 Small posterior capsular opacity lightly nasal to center of the lens—Mittendorf dot

abnormalities are likewise diagnosed shortly after birth. Others, in whom the size of the eye is normal and abnormalities are restricted to the posterior aspect of the lens or the posterior pole of the eye, may escape early detection, especially if the red reflex is not carefully evaluated by the pediatrician or primary caregivers and may present much later with strabismus or through a failed vision screening examination. Finally, patients with very mild variants such as very small remnants of the pupillary membrane, Mittendorf dots (Fig. 20.2) or Bergmeister papilla (Fig. 20.3) may be identified on routine eye examinations at any age.

The breadth of clinical findings due to the extent of residual fetal vasculature has led to a tripartite classification system (Table 20.1). Anterior PFV refers to malformations and secondary complications due to involvement of the anterior chamber, iris, and lens by the partially regressed tunica vasculosa lentis and hyaloidal vascular system. As such, it includes cases of congenital cataract, remnants of the pupillary membrane (Fig. 20.2), and some cases of localized coloboma of the lens (Fig. 20.4). The latter are due to interference with the formation of the zonule in a sector of the lens by an irido-hyaloid vessel that has not regressed and exerted localized deformational pressure on developing zonular apparatus. Patients previously referred to as having PHPV generally have unilateral microphthalmia, cataract caused by fibrosis

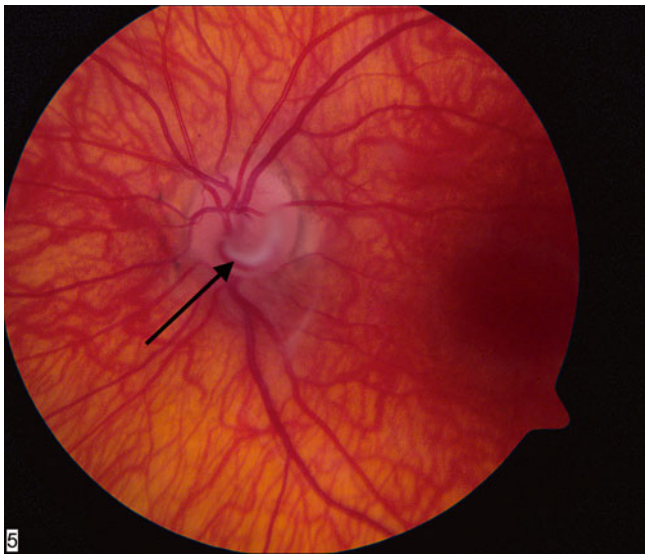

Fig. 20.3 Small posterior remnant of the regressed hyaloid system at the disk (*arrow*)—Bergmeister papilla

Table 20.1 Clinical varieties of persistent fetal vasculature with corresponding anterior, posterior, and combined categories (modified from Ceron et al. [4])

PFV variety	Anterior	Posterior	Combined
Persistent pupillary membrane	x		±
Coloboma of the lens	x		
Mittendorf dot/brittle star formation	x		±
Elongated ciliary processes	x		±
Shallow anterior chamber	x		±
Intracapsular and retrolental fibrovascular membrane	x		±
Microphthalmos with vitreous stalk and lens abnormalities (PHPV)	x	x	x
Cataract	x	x	x
Leukocoria	x	x	x
Intralenticular hemorrhage	x	x	±
Coloboma of the lens	x		
Bergmeister papilla		x	±
Retinal fold		x	±
Optic nerve hypoplasia/dysplasia		x	±
Hypoplastic macula; pigment maculopathy		x	±
Vitreous membranes and stalk		x	±

PFV persistent fetal vasculature, *PHPV* persistent hyperplastic primary vitreous

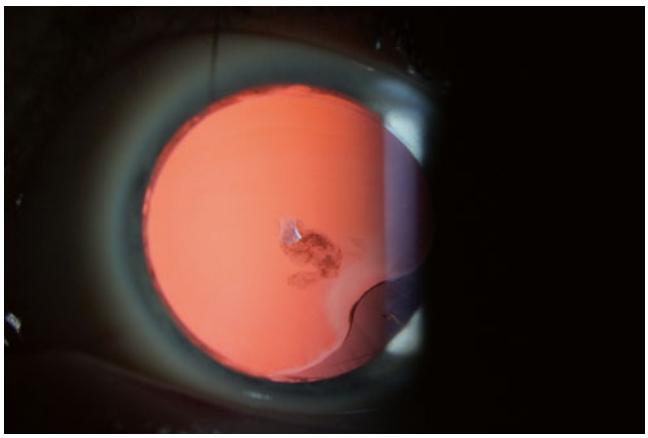

Fig. 20.4 Notched equator of the lens at 4 o'clock with absent zonules (coloboma of the lens). There also is a small central capsular opacity

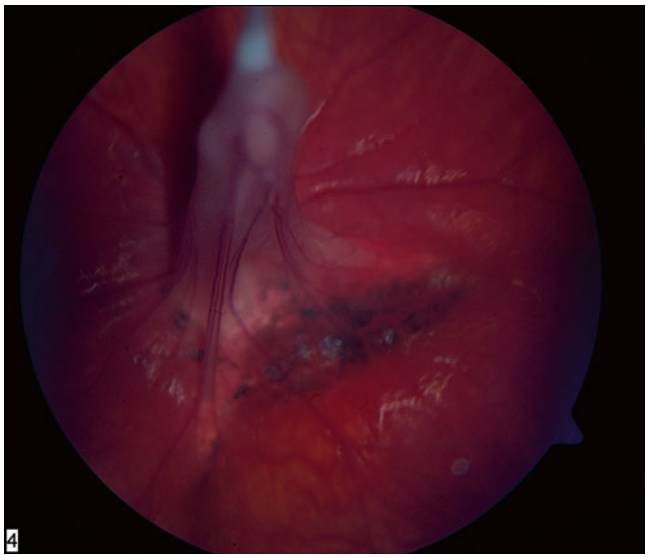

Fig. 20.5 Posterior PFV at the disk the stalk protrudes forward. The traction has resulted in pigmentary changes near the dysplastic disk

in and on the posterior capsule of the lens, and dragging of the ciliary processes toward the center of the posterior lens capsule. Persistence of the fetal vasculature posteriorly classically causes changes to the lens, optic nerve, and/or retina, resulting in optic nerve dysplasia, retinal folds, and/or posterior stalks (Fig. 20.5). Patients with combined forms of PFV demonstrate features of both categories, and almost always have microphthalmia, cataract, leukocoria, and sensory strabismus. More than 60 % of patients with PFV fall under the combined PFV category [2, 3]. Persistent fetal vessels from the iris that lead to adhesions to the corneal endothelium cause focal areas of corneal opacification, as seen in some cases of peripheral Peters' anomaly [1]. Similarly, abnormal blood vessels causing malpositioning of the iris stroma can cause congenital ectropion uvea or radial fibrous bands that deform the iris. Incompletely regressed irido-hyaloidal vasculature can cause focal zonular and lenticular maldevelopment, leading to what has been referred to as lens coloboma, and occasionally lens subluxation [1].

Associated Syndromes

In its strict definition, PFV is a unilateral, idiopathic, and non-inherited condition. However, the similarity of PFV to other vascular and malformative ocular diseases that occur in heritable systemic diseases such as Trisomy 13, Norrie disease, Walker–Warburg syndrome, incontinentia pigmenti, and oculo-dento-osseous syndrome has led to the inaccurate use of the PFV terminology in the context of heritable conditions.

Pathogenesis

Embryology

Development of the eye begins within the first few weeks of embryogenesis and is highly dependent on the growth of a luxuriant, but transient anastomotic network of blood vessels that develops posteriorly to anteriorly. Three weeks after fertilization, the future hyaloidal artery, arising from the ophthalmic artery, enters the eye inferiorly by means of the fetal fissure and grows through the vitreous compartment toward the posterior aspect of the fetal lens, forming the posterior tunica vasculosa lentis. This structure nourishes the developing optic cup posteriorly, and anastamoses anteriorly with the annular artery via irido-hyaloidal vessels to create the anterior tunica vasculosa lentis, which develops alongside the pupillary membrane in the iris stroma by the 6th to 7th week of gestation (Fig. 20.6).

This complex vascular network is most extensive between the 8th and 12th weeks of development, and slowly begins to regress in the 2nd trimester, with almost complete involution at birth. In most cases, the anterior portion involutes at 8 months, while the posterior portion of the system typically regresses later, although the anterior and posterior hyaloidal systems may persist independently or together [4]. As this vasculature develops and regresses, the vitreous is also continually changing. The primary vitreous develops from embryonic mesenchymal cells and contains the hyaloidal vasculature described above. The secondary vitreous begins to develop in the 9th week of gestation from the inner retinal cells, depositing centrally from the ocular wall. In normal development, the secondary vitreous compresses the primary vitreous into what is known as Cloquet canal, leading to regression of the vascular structures. Normal growth of the eye depends in part upon expansion of the secondary vitreous,

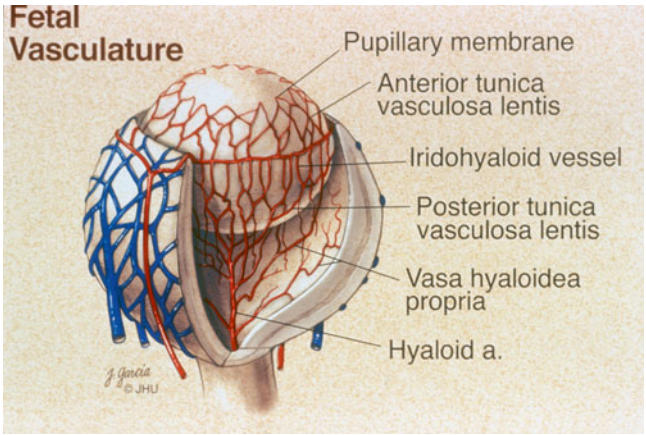

Fig. 20.6 Anastomotic relationships of key components of the fetal vasculature. Reproduced with permission from Ref. [1]

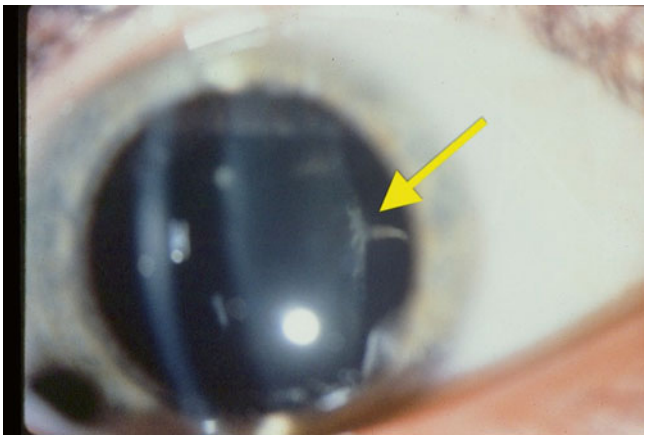

Fig. 20.7 The anterior end of the hyaloid remnant divides as it attaches to the back of the lens forming a so-called starfish (*arrow*)

which explains why many eyes with PFV are microphthalmic. By the 23rd week of gestation, well-formed fibrils running from the ciliary epithelium to the lens are identifiable, better known as zonules, or the tertiary vitreous [5].

Incomplete regression of the fetal vasculature occurs in 3 % of normal full-term babies and in 95 % of premature babies, leading to small remnants such as the Mittendorf dot—a small remnant on the posterior aspect of the lens, brittle star (Fig. 20.7) sign—a multi-pronged opacity that connects the hyaloid remnant to the back of the lens, Bergmeister papilla—a small veil on the surface of the optic disk, and persistent pupillary membranes that float in the anterior chamber or adhere to the anterior surface of the lens [3].

Molecular Genetics

Despite the clinical descriptions of the broad spectrum of clinical phenotypes of PFV, the molecular mechanisms leading to the persistence of the fetal vasculature have been elusive. Although it has been hypothesized that regression of the hyaloidal vessels is regulated by a complex pathway of angiogenic and apoptotic signals, only recently have attempts successfully uncovered pieces of the puzzle. Recent work in animal models strongly implicates the *arf* (alternative reading frame) protein, and p53 in the pathogenesis of PFV [6]. In mouse eye development, the *arf* tumor suppressor gene promotes hyaloidal vessel regression, indicating that its deficiency could cause persistence of the fetal vasculature [6, 7]. Similarly, p53 is key in a critical apoptotic pathway, leading to the hypothesis that mutations in p53 lead to incomplete regression due to failure of appropriate apoptosis [8, 9]. The WNT signaling pathway is also an important signaling system and involves a number of proteins, including norrin (pathogenic to Norrie disease), and frizzled-4 receptor (FZD4, linked to pathogenesis of FEVR). Mutations in the genes coding for these proteins have been described in a limited number of unilateral and bilateral cases of PFV, providing supportive evidence that inhibition of apoptotic signaling leads to persistence of the fetal vasculature, as well as to other related syndromes such as Norrie disease, FEVR, and ROP [10, 11].

Clinical Genetics

The majority of cases of PFV are sporadic and non-heritable. Studies in dogs and cats, as well as case reports in humans, indicate the possibility of rare autosomal recessive, X-linked, and dominant variants [4, 7, 8, 12, 13]. Linkage analysis in cases of autosomal recessive PFV suggests that a possible candidate gene is located on chromosome 10q11-q21 [4, 7]. Similarly, two case reports of PFV in the absence of other congenital anomalies and with a family pedigree suggestive of AD transmission have been described, but no candidate genes were identified [8, 12].

Differential Diagnosis

Retinoblastoma is a retinal tumor of children, caused by mutations in the *RB1* gene located on chromosome 13. Retinoblastoma is predominantly identified in children age 6 months to 2 years who present with leukocoria and a retinal mass. Occasionally, differentiating retinoblastoma from PFV can be challenging. The eye in retinoblastoma is not microphthalmic and has no cataract, and ultrasonography or computed tomography typically reveals calcification in retinoblastoma but not in PFV.

Coats' disease is a congenital, non-hereditary disease of the retinal vasculature, associated with vascular leakage, retinal exudates, and retinal detachment, usually occurring in

males. When Coats' disease is strongly suspected, some advocate sending samples of subretinal fluid for analysis of presence of fatty exudates, ghost cells, and cholesterol crystals. Coats' disease can be distinguished from PFV by the presence of extreme subretinal exudation, and large areas of telangiectasia and retinal neovascularization.

Familial exudative vitreoretinopathy (*FEVR*) is a congenital, inherited disease of the retina caused by failure of peripheral retinal vascularization. Although it mimics retinopathy of prematurity, as well as Coats' disease and peripheral uveitis, FEVR occurs in full-term babies without a history of oxygen supplementation. FEVR is usually distinguished from PFV by evidence of family history and bilateral, though sometimes markedly asymmetric, disease.

Norrie disease is a rare X-linked recessive disease, also known as oculo-acoustico-cerebral degeneration, presents as a variable triad of retinal malformation or dysplasia, deafness, and mental retardation. It often has retinal findings that mimic PFV, including retinal folds, retrolental mass, microphthalmia, cataracts, and secondary glaucoma, but it is usually distinguished from PFV by its X-linked inheritance, bilaterality, and systemic manifestations.

Retinopathy of prematurity (*ROP*) if diagnosed late with end-stage findings such as total retinal detachment and posterior membranes can mimic PFV. However, it is usually distinguished by its bilaterality and occurrence in premature, low birth weight infants exposed to high levels of oxygen supplementation.

Ocular toxocariasis is an infectious disease of the retina caused by ingestion of Toxocara cysts, in which patients commonly present with a large glial mass coming off of the optic nerve. Late stage disease can present with retinal folds, or total retinal detachment. Because infection depends upon ingestion of feces of infested dogs, it usually presents in children who are older and more mobile (aged 4–8 years) than the typical patient with retinoblastoma.

Retinal detachment in the newborn and infant population is rarely a spontaneous event. More commonly, it is associated with a predisposing disease such as those listed above. However, in the absence of other identifiable causes of a retinal detachment, spontaneous detachment could mimic PFV, but would be readily distinguishable based on the clinical context, and absence of other ophthalmic findings such as those described in Table 20.1.

Diagnostic Methods

The key to the diagnosis of PFV is a careful and thorough clinical examination with appropriately selected testing modalities. Although most cases of PFV can be diagnosed on the basis of clinical exam alone, there are a variety of supplemental tests that may prove helpful in cases with challenging presentations. B-scan ultrasonography is critical if the view into the posterior segment is poor (Fig. 20.8). Anterior segment OCT can provide important information about the ciliary body and structures under the peripheral iris. In select cases, fluorescein angiography may be a useful test to identify patent irido-hyaloidal vessels. Although computed tomography is rarely necessary to make the diagnosis of PFV, radiographic scans through the orbit can detect the presence of calcification, the absence of which is more suggestive of PFV. Additionally, color-flow doppler sonography can be used to characterize the vascularity of PFV stalks [14].

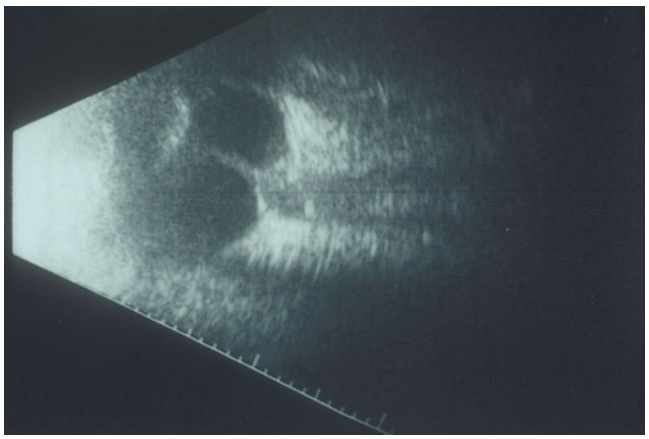

Fig. 20.8 B-scan of an eye with combined posterior and anterior PFV. There is apparent localized detachment at the optic nerve head forming a tent that attaches via a thick membrane/hyaloid remnant to the posterior aspect of the lens

Treatment

The management of PFV has evolved as the understanding of the disease and its various forms has improved. Each case requires an individual assessment of the goals for visual rehabilitation, as well as risks of any and all interventions, including observation.

Without treatment, all eyes with PFV that obscures a view of the fundus develop severe amblyopia, along with the associated risk of strabismus. One feared scenario likely due to growth of the lens is progressive shallowing of the anterior chamber, leading to angle closure in these small eyes, elevation of intraocular pressure, infarction of the ciliary body, vitreous hemorrhage, retinal detachment, and phthisis bulbi. In the 1970s, natural history collected on patients with PFV showed that enucleation was a common endpoint for these eyes due to intractable glaucoma and phthisis [3]. It is for these reasons that many advocate at least lens removal in certain cases of PFV, even if the prognosis for visual improvement is dismal.

Surgical Intervention

The decision to proceed with surgery usually depends upon the severity of presentation, as well as the patient's age, and visual prognosis. Common indications for surgery include a visually significant cataract, shallowing of the anterior chamber, intralenticular hemorrhage, traction on the ciliary body, and elevated intraocular pressure. Important considerations for surgical planning include awareness of the fact that the pars plana is not as well developed in an infant as it is in an adult, as well as cognizance of the strength of vitreoretinal adhesions, and the thick leathery consistence of the posterior lens capsule.

One of the utilized surgical options employed for patients with isolated posterior, and for the rare combined severe cases of PFV is a closed pars plana vitrectomy, lensectomy, and membranectomy. Patients with predominantly anterior PFV, including those with lens involvement and just a thin strand that bridges the optic nerve to the back of the lens, however, are best managed with a lensectomy via a limbal approach. Both techniques have the advantages of good visualization through a clear cornea. Factors thought to increase intraoperative and post-operative complications include the width of the fibrovascular stalk, presence of blood flow in the stalk, combined type of PFV, and microphthalmia [15]. Surgeons should be prepared to deal with thickened and difficult to cut posterior capsules and with ciliary processes that are pulled toward the center of the contracted posterior capsule. A few maneuvers are worth mentioning that facilitate the attainment of a large clear pupillary axis. After the anterior capsule is opened and the cortex removed, any blood vessels in the posterior capsule are cauterized using an intraocular cautery (Fig. 20.9); the posterior capsule is stabbed with an MVR blade; it is then divided into small segments using curved intraocular scissors and the capsular fragments are removed with the vitrector. The posterior capsule is divided radially all the way to the equator and in-between the ciliary processes in multiple quadrants (Figs. 20.10 and 20.11), and the segments are then removed using the vitrector [16]. For a video demonstration visit (https://vimeo.com/4405171). Post-operative management is similar to that for patients who have had cataract extraction and routinely includes anti-inflammatory medications, antibiotics, patching to prevent amblyopia, and aphakic correction, either with contact lenses or spectacles.

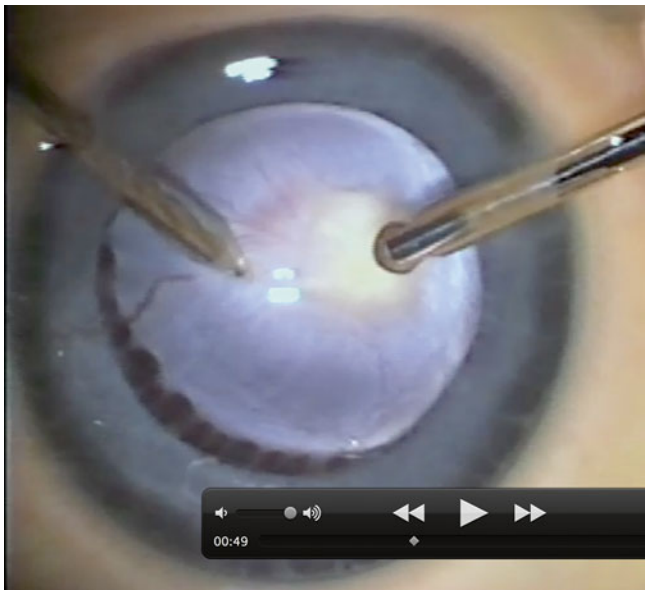

Fig. 20.9 Intraoperative photograph shows fibrotic posterior capsule with intracapsular blood vessels. Intraocular cautery cauterizes one of the larger vessels. The other instrument provides irrigation. The ciliary processes are pulled inferiorly toward the posterior capsule

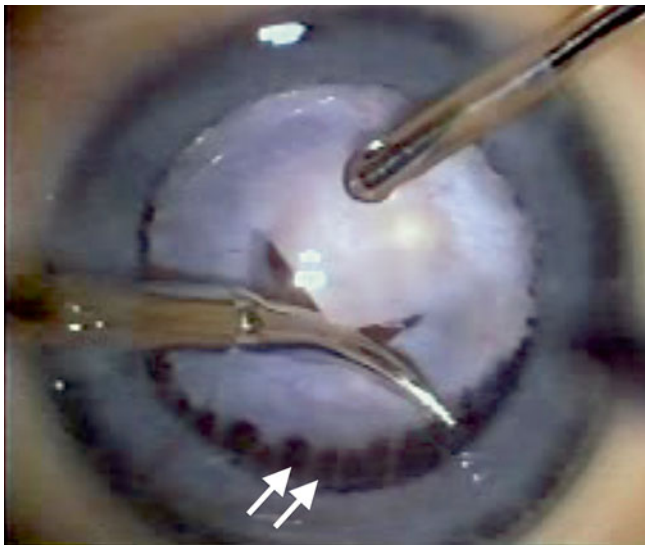

Fig. 20.10 Intraocular scissors are used to divide thick fibrotic posterior capsule all the way to the edge of the capsule between ciliary processes. Double arrows indicate elongated ciliary processes

Outcomes

Visual outcomes correlate strongly with the type and severity of the PFV, as well as the age at presentation [17]. In general, patients with anterior PFV fare better than those with combined or posterior forms of the disease. Those who are diagnosed and managed at a younger age tend to obtain better functional and anatomic outcomes. Patients who undergo surgery with the hope of obtaining good vision require dedicated families committed to long-term amblyopia therapy, including aphakic correction and patching. In the absence of these interventions, prognosis for good vision is guarded.

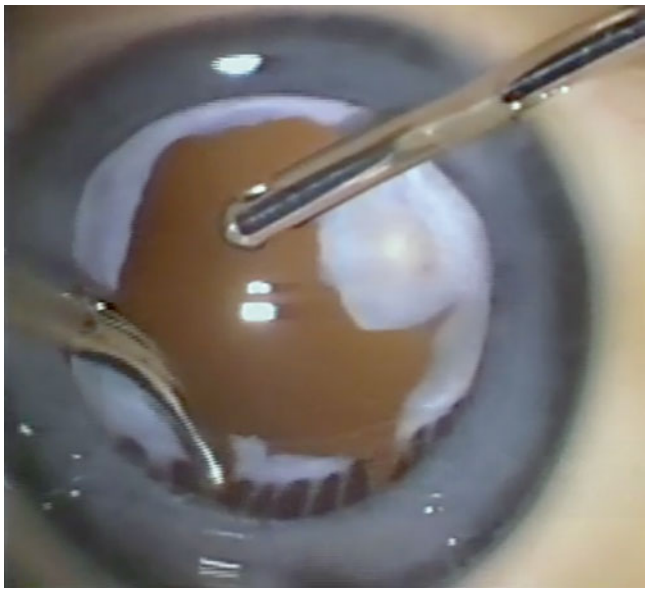

Fig. 20.11 More advanced stage of surgery shown in Figs. 20.8 and 20.9. An additional cut is taken between ciliary processes and a large part of the posterior capsule has been removed. This maneuver is repeated several times until the tight capsular ring is divided and the ciliary processes fall back in place and most of the capsule is removed

Illustrative Case

A 6-day-old newborn was referred to Ophthalmology for assessment of a cataract in the left eye. On examination, the cornea was noted to be slightly small at 9.5 mm in diameter, with mild ectropion uveae at 9 o'clock, a moderately deep anterior chamber, and a dense cataract with no view to the posterior pole. B-scan ultrasonography revealed a faint opacity extending from the disk to the anterior vitreous, but no retinal traction or detachment. The child was taken to the OR for lensectomy and removal of the retrolental stalk at 6 weeks of age. A clear corneal anterior surgical approach was undertaken. The anterior capsule was opened using the vitrector and an MVR blade. The capsulotomy was enlarged and the cortical material irrigated and aspirated. The posterior capsule was found to be white and thickened, and upon incision, a retrolental vessel was visualized and cauterized with intraocular cautery. The posterior capsule was divided using intraocular scissors and the vitrector. No complications were encountered. The patient's aphakia was corrected using a contact lens and patching was instituted. At the age of 3 years visual acuity in the operated eye was 20/50.

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