Persistent Fetal Vasculature Syndrome

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Abstract

Persistent fetal vasculature (PFV) syndrome represents a broad spectrum of abnormalities that involve varying degrees of fetal hyaloid system remnants and affect almost all parts of the eye. Although the disease has long been recognized in the differential diagnosis of leukocoria, and diagnostic and treatment modalities, as well as our understanding for PFV, have evolved over the years, the full spectrum of findings is still not fully appreciated and the disease continues to present with surprises. This heterogeneity of the disease makes the diagnosis and the management challenging. This chapter presents the current information on important aspects of PFV and provides a comprehensive guide for ophthalmologists, from the recognition of PFV and associated anatomic variations to surgical indications and techniques, and postoperative expectations.

Keywords

Persistent fetal vasculature · Persistent hyperplastic primary vitreous · Microphthalmia · Tractional retinal detachment · Leukocoria · Peripheral retinal elongation · Lens sparing vitrectomy · Lensectomy · Vitrectomy · Amblyopia management · Closed funnel retinal detachment · Tent like tractional retinal detachment · Combined hamartoma of retina and retina pigment epithelium

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Introduction

Persistent fetal vasculature (PFV) syndrome is a congenital developmental abnormality caused by failure of programmed involution of the primary vitreous and hyaloid vasculature. It was first described by Reese in 1955 as a congenital malformation of the anterior portion of the primary vitreous and referred as "persistent hyperplastic primary vitreous" for a long time [1]. However, because "primary vitreous" refers only to retrolental hyaloid vessels, and the condition involves the persistence of both hyaloid vessels and tunica vasculosa lentis (TVL), Goldberg renamed the condition with the more comprehensive term "persistent fetal vasculature" in 1997 [2].

PFV typically presents unilaterally in full-term infants without associated systemic findings, but rarely it may occur in conjunction with systemic syndromes such as Walker- Warburg syndrome [3], Aicardi syndrome [4], trisomy 13, 15, 18 [2, 5] and may be bilateral [6]. Overall, bilateral cases account for less than 10% of the cases. The exact etiology of PFV is still largely unknown. Most of the cases are sporadic. However, rare cases of autosomal dominant and autosomal recessive inheritance have been reported related to the genes NDP and ATOH7 [7, 8].

Normal Embryology

In order to appreciate the disease process of PFV, it is necessary to understand the development and normal regression of the entire fetal intraocular vasculature, the primary function of which is presumed to nourish the developing lens prior to the production of aqueous humor [9] (see also Sect. 1, Chap. 1).

The development of intraocular vascularization is initiated when the hyaloid artery, which is the distal portion of the ophthalmic artery, enters the eye via the fetal fissure at 3 weeks' gestation [10]. The artery traverses to the developing lens over the course of the next week and arborizes to eventually form the posterior tunica vasculosa lentis, a capillary meshwork closely surrounding the posterior pole of the developing lens [9, 11, 12]. The posterior TVL passes along the lens equator as a set of parallel, straight, nonbranching vessels, forming the lateral tunica vasculosa lentis, also known as iridohyaloid vessels (normal regression of which allows space for the development of zonular apparatus). Concurrently, at the anterior edge of the optic cup, vessels form anastomoses to create annular vessel. By 5 weeks' gestation, the hyaloid artery gives off multiple branches 3–4 mm behind the lens which resemble struts of an umbrella and develop into the vasa hyaloida propria [9–11]. At this stage, the primary vitreous is also developing as the hyaloid artery system develops. By 6–7 weeks' gestation, the anterior TVL forms on the anterior surface of the lens by the looping branches of the annular vessel and associated mesoderm [9]. The mesodermal elements are destined to grow into the pupillary area to form pupillary membrane while the vascular loops regress [2].

From 8 to 12 weeks' gestation, this complex vascular system reaches its most extensive state of development, and the lens is completely encircled by the TVL [13].

Subsequently, at the beginning of the second trimester, regressive events initiate posteriorly, first in the hyaloid artery and in the vasa hyaloida propria, then the posterior TVL, and the iridohyaloid vessels [2, 13]. As the hyaloid system starts to involute, the secondary vitreous continues to grow and primary vitreous assumes a cone shape with an apex at the disc and a base at the posterior surface of the lens.

During the fifth month, the anterior TVL disappears, and the pupillary membrane continues to develop. The primary vitreous retracts further centrally creating Cloquet's canal. The hyaloid system continues to involute and is usually totally regressed at 28 to 30 weeks' gestation [2, 14]. However, the remnants of the hyaloid vessels can exist within the Cloquet canal after birth. The pupillary membrane shows variable regression and may also persist normally after birth [2].

Clinical Presentation

PFV syndrome has a spectrum of presentations determined by the degree of involution of the hyaloid and TVL. Although most of the spectrum affects both anterior and posterior segments to some extent, eyes with the persistence of predominantly hyaloid vasculature are classified as posterior PFV, and those with the persistence of predominantly TVL as anterior PFV [2]. Nevertheless, most of the cases exhibit features of both anterior and posterior forms and classified as mixed or combined PFV [6, 9]. The disease can also occur in conjunction with other ocular abnormalities, including Peter's anomaly, microcornea, uveal coloboma, and morning glory disc anomaly [2, 15–18]. Variety of such presentations makes PFV challenging for surgical management.

1. **Anterior PFV**

The predominantly anterior form characteristically presents with leukocoria shortly after birth (Fig. 30.1a, b). Leukocoria is often due to a retrolental fibrovascular membrane, either alone or in combination with a cataractous lens. The retrolental membrane is caused by the persistence of posterior TVL and may vary in size and shape (Figs. 30.1c–e, 30.4c, 30.10, 30.12, 30.13 and 30.14) [2]. It may incorporate into elongated and centrally dragged ciliary processes and peripheral retina (Figs. 30.10, 30.11, 30.12, 30.13 and 30.14) [5, 15, 16, 18]. The eye is often microphthalmic (Fig. 30.1a, b); however, this may be subtle. Persistent pupillary membrane and strands, prominent and dilated radial iris vessels, and hairpin loops may be observed in some cases (Figs. 30.1c–e and 30.14), related to the persistence of anterior TVL and iridohyaloid vessels. Occasionally, the pupil may be deformed by the arborizing iris vessels, leading to small sphincter notches, corectopia, or congenital ectropion uveae [14]. The anterior chamber may be shallow due to swollen and anteriorly-shifted lens, extensive posterior synechiae (Fig. 30.1c–e),

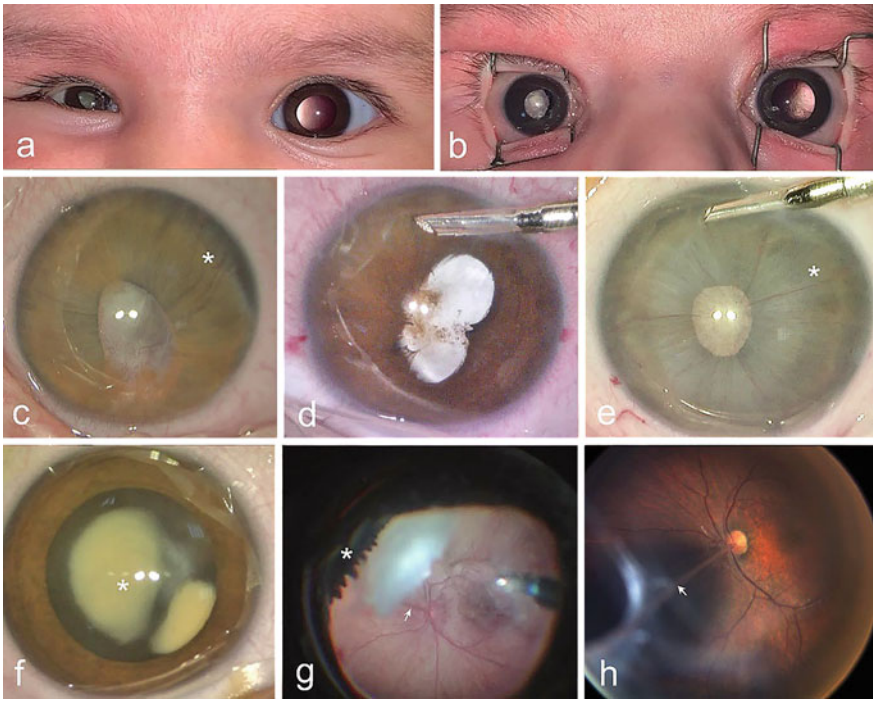

Fig. 30.1 Anterior segment findings of PFV: (**a**, **b**) Microphthalmia and leukocoria. (**c**–**e**) Severe anterior PFV cases with radial iris vessels (*), posterior synechia and totally white opaque lens including vascular elements in it. (**f**) Anterior PFV presenting with whitening at the back of the lens that is secondary to an old dehemoglobinized retrolental hemorrhage (*). Note the periphery of the lens is mostly clear. (**g**) Prominent ciliary processes (*) and a thin hyaloid remnant (arrow) in an anterior PFV case (**h**) Mild anterior PFV with a thin and eccentric hyaloid artery connection to the back of the lens (arrow)

and peripheral anterior synechiae, which often progress to secondary angle-closure glaucoma. Unlike the common observation of microphthalmos, patients who develop glaucoma may present with normal-sized or buphthalmic eyes (Fig. 30.9).

Hyphema may be found in some cases, associated with the fine vessels of persistent anterior TVL. Retrolental hemorrhage (between the posterior lens surface and the fibrovascular plaque) may also be seen in some of the cases during the course (Figs. 30.1f and 30.2). Congenital lens subluxation may rarely occur if zonular maldevelopment due to persistent iridohyaloid vessels is severe. Posterior lenticonus may also develop because of hyaloid artery traction on an inherently weak posterior capsule [19]. Although quite infrequent, the hyaloid artery may cause enough traction to cause a full-thickness posterior capsule defect yet it may still resorb during development. This may cause migration of lens particles through a defective posterior capsule, producing a pseudo-hyaloidal stalk appearance (Fig. 30.15, see **Video** 1) [20]. On rare occasions, the lens may contain

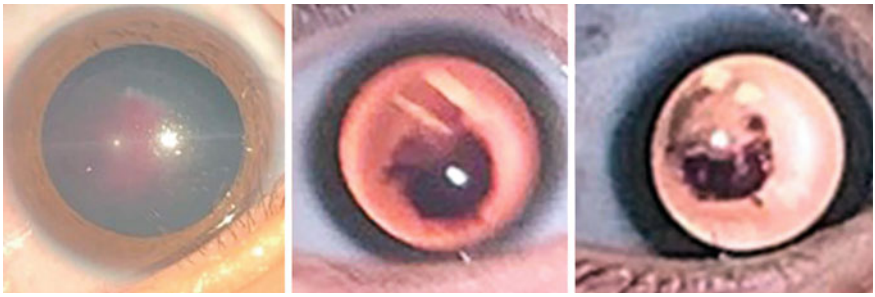

Fig. 30.2 Hemorrhage at the back of the lens which cleared totally leaving a clear lens within time following a lens sparing vitrectomy for the tent-like TRD associated with PFV

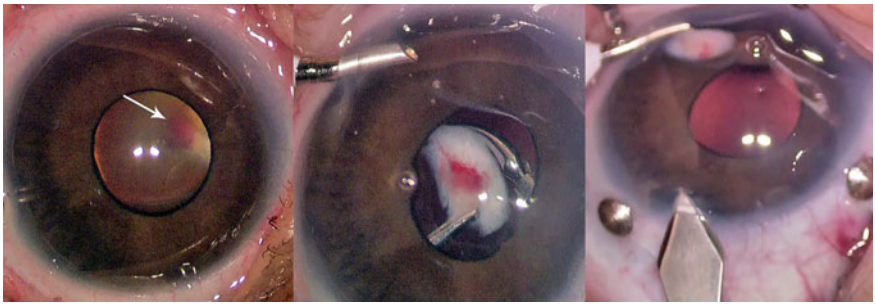

Fig. 30.3 Removal of a choristomatous (cartilage-like) plaque (arrow) through the anterior chamber as a foreign body, which could not be eaten with a vitreous cutter during lensectomy and had to be cut from the sides with curved scissors and to be removed from a limbal corneal incision

choristomatous tissue such as cartilage which cannot be removed with a vitreous cutter and require removal through the anterior chamber as a foreign body (Fig. 30.3). The posterior pole, optic nerve, and macula may be normal in the purely anterior forms without any evidence of a retinal fold. However, a thin hyaloid stalk generally extends from the optic nerve head with the anterior end lying freely in the vitreous gel even in purely anterior forms (Fig. 30.1g, h).

2. **Posterior PFV**

The posterior subtype consists of an elevated epiretinal or vitreous membrane and a stalk from the optic nerve, retinal fold, or tractional retinal detachment (TRD). The stalk itself may be a simple column-like structure extending between the lens and the optic nerve or posterior retina, or it can be an inverted Y shaped with a second or even third arm attaching to the disc and other areas of the retinal surface (Figs. 30.4, 30.5a, 30.6 and 30.16, see **Video** 2). The stalk exerts traction on the retina, resulting in areas of tent-shaped TRD. Some of these cases show overlapping features with the peripapillary combined hamartoma of the retina and retinal

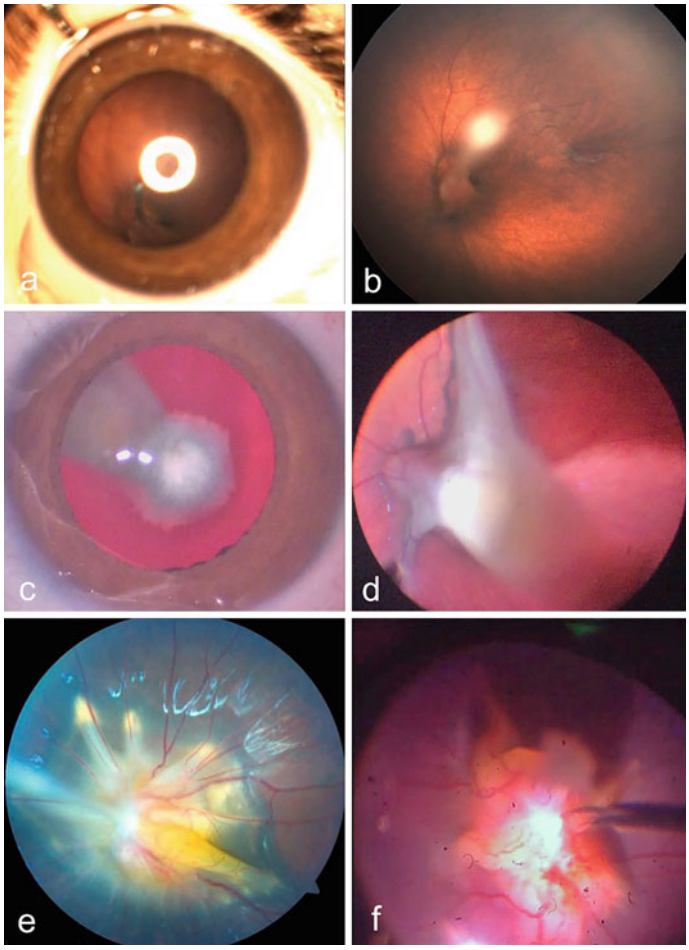

Fig. 30.4 Posterior PFV cases of varying severity: (**a**, **b**) An isolated mild posterior PFV case with a hyaloid stalk that has a narrow base and apex, causing a peripapillary limited tenting and a tiny retrolental opacity. (**c**, **d**) A mixed type PFV with centrally located retrolental plaque and multiple attachment points on the retina. (**e**, **f**) Examples of moderate tent-shaped posterior PFV cases

pigment epithelium (CHRRPE). Both of the diseases have an appearance of elevated mass lesion at the optic nerve that extends in a fanlike projection towards the periphery and associated with greyish pigmented dysplastic retina and tortuous retinal vessels (Fig. 30.5). Differently than CHRRPE, we see a stalk extending anteriorly from the apex of the elevated tissue in PFV cases. This phenotypic similarity between the diseases may suggest a shared origin of disturbance in the development period and may represent different ends of a disease spectrum and needs further investigation.

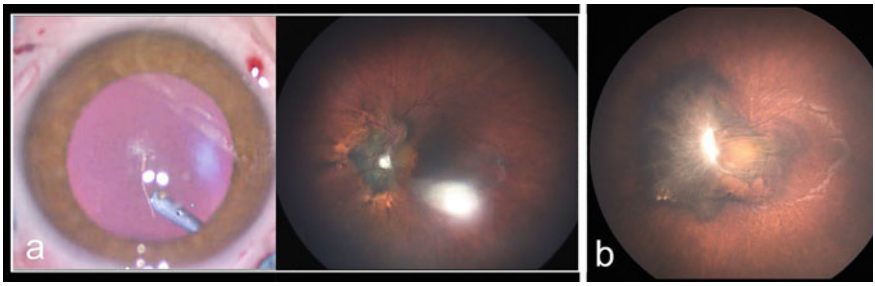

Fig. 30.5 Phenotypic similarity between posterior PFV (**a**) and combined hamartoma of the retina and retinal pigment epithelium (**b**)

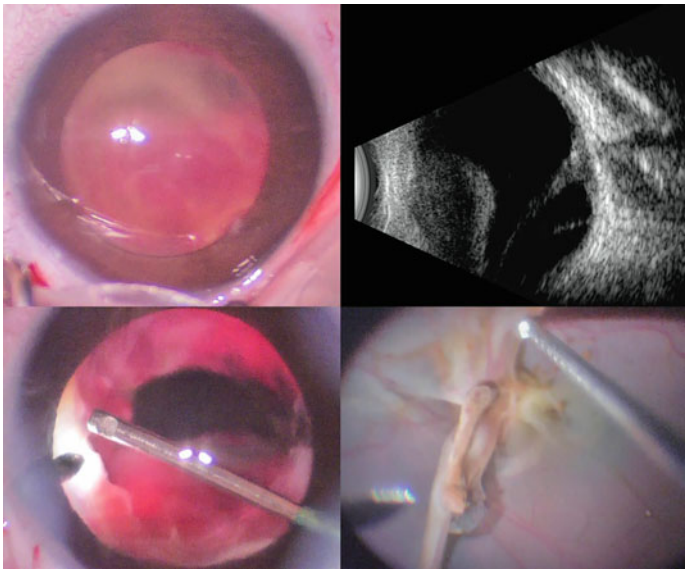

Fig. 30.6 Posterior PFV case presenting with retrolental and vitreous hemorrhage. B-scan ultrasonography revealed multi-rooted stalk and vitreous membranes. A limbal lensectomy vitrectomy surgery was performed. Following layer-by-layer removal of dense hemorrhagic membranes, a hyaloid stalk was observed extending from the optic nerve head and forming retinal folds in all directions

Although the type of retinal detachment in PFV is primarily tractional in origin due to the adhesion of fetal tissue to the developing retina, it may subsequently develop rhegmatogenous characteristics as well. Patients may also develop vitreous hemorrhages (Fig. 30.6). The optic nerve and macula may be primarily hypoplastic or dysplastic. Traction from posterior components of the primary vitreous may further contribute to these structures' dysfunction and abnormal shape, causing changes such as macular ectopia or failure of development of foveal pit.

The eye is usually microphthalmic but may be of normal size. The lens is often clear in the purely posterior subtype; however, it may be associated with a focal lens opacity at the site of attachment of the stalk (Figs. 30.4a, 30.5a and 30.16) or become cataractous over time if the vessels from the membrane expand forward enough to enter the lens via the posterior capsule.

3. **Mixed Type PFV**

The posterior subtype rarely presents as a pure posterior form with no anterior involvement. Rather, it is often accompanied with persistence of TVL and/or some degree of lens opacity. The eyes that harbor both anterior and posterior segment involvement to a clinically significant extent are classified as *mixed PFV subtype*. As described in the previous paragraphs, the hyaloid stalk exerts traction on the retina causing TRD. The TRD most commonly presents in a *tent-like configuration* (Figs. 30.4, 30.5a, 30.7a and 30.16) and rarely in a *closed-funnel* configuration in the most severe forms of the disease (Figs. 30.7b and 30.17, see **Video** 3).

Tent-shaped morphology is the most typical and common presentation of the posterior disease and shows a better prognosis than the closed funnel form. The release of tractions with surgery often allows the anteriorly pulled-tented retina to return to a more normal anatomical position and function. Literature data show significant reversal of dragging and reattachment of the retina in up to 77% to 91% of these cases and gaining of counting fingers or better vision that range between 42–82% [17, 21–24]. In our series of 30 eyes with tent-shaped posterior PFV, 27 (90%) showed significant reversal of tenting. Except for two cases with persistent macular folds, complete macular reattachment was obtained in all, and 21 eyes (70%) achieved counting fingers or better vision in a follow-up over one year [18].

Closed-funnel shaped posterior PFV, on the other hand, is a rare phenotype associated with very poor prognosis. These cases tend to be bilateral and mostly associated with total cataractous/membranous lens, posterior synechia, shallow anterior chamber, corneal opacification and microphthalmia. Literature research suggests that these cases are often enucleated with the concern of retinoblastoma or

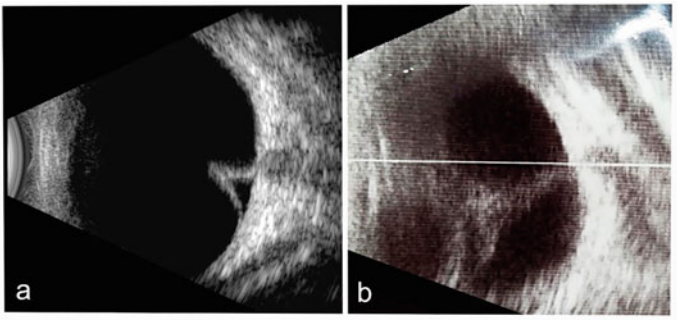

Fig. 30.7 B-scan ultrasonography shows tent-shaped retinal detachment (**a**) and closed funnel-shaped retinal detachment (**b**) in two cases with mixed type PFV

Fig. 30.8 An 18-month-old baby girl with severe form of mixed PFV coming for a second opinion to reverse the increasing corneal opacification in the left eye that causes worsening cosmetic problem every month. B-scan ultrasonography revealed a closed funnel retinal detachment. Note the large central corneal opacification (**a**) secondary to irido-lenticulo-corneal adhesion, which was significantly reversed after lensectomy done for cosmesis. (**b**) Picture taken 6 months after the operation shows a central leukocoria with very mild corneal edema in the left eye. The parents were very satisfied with the cosmetic result

considered inoperable [1, 25–27]. However, the natural course of untreated closed-funnel posterior disease is characterized with progressive deterioration of the globe [1, 16, 25, 28]. These eyes eventually develop corneal opacification, glaucoma, or phthisis bulbi if left untreated. Surgery may prevent these complications and maintain the globe in a more acceptable cosmesis (Figs. 30.8, 30.17). In eyes with shallow anterior chamber, even lensectomy with synechiolysis may prevent further corneal opacification and partially reverse pre-existing opacities. In our series of 22 eyes with closed funnel-shaped PFV, 73% had a formed globe with acceptable cosmesis; apparent leukocoria resolved in 41%; and 45% achieved light perception vision after surgery [18].

Diagnosis

The best diagnostic method is the direct visualization of any component of the persistent vascular remnants. While visualization of the retrolental area may frequently be blocked due to cataracts or synechiae, careful examination of the iris may reveal an iridohyaloid vessel, a small notch or indentation at the pupil margin, or a pupillary membrane. Although not pathognomonic, elongated and prominent ciliary processes are also particularly specific. Presence of such signs should raise the clinician's suspicion, especially when combined with microphthalmia or microcornea.

B-scan ultrasonography is extremely helpful to assist with diagnosis of the eyes with a limited or absent fundus view (Fig. 30.7). Apart from demonstrating the vitreous stalk from the posterior pole to the lens, it can also provide information about the axial length, lens status, presence of retinal detachment and calcification which is very important for differential diagnosis of retinoblastoma. However, B-scan ultrasonography may still miss the hyaloid artery stalk if it is very thin.

Although infrequently used, fluorescein angiography (FA) can also be helpful to delineate abnormal fetal vasculature such as iridohyaloid vessels, hairpin loops around the pupil, radially oriented retrolental vessels (also known as the brittle-star), remnants of vasa hyaloidea propria and hyaloid artery. It may also assist in the differential diagnosis.

Differential Diagnosis

Since the most widely recognized clinical presentation of PFV is leukocoria, the differential diagnosis should include diseases causing a white pupil.

- The most important of these is undoubtedly retinoblastoma, which is the most common intraocular tumor of childhood, and delayed or erroneous diagnosis can lead to grave consequences. In general, PFV eyes are often microphthalmic, while eye size is normal in retinoblastoma. In case of diagnostic difficulty, B-scan ultrasonography and computed tomography (CT) may be helpful. Calcification observed on these imaging studies suggests malignancy; however, magnetic resonance imaging (MRI) may be a better alternative to CT scans because of the potential increased risk of malignancy with ionizing radiation (Table 30.1).
- Other causes of leukocoria; congenital cataracts, familial exudative vitreoretinopathy (FEVR), Coats' disease, retinopathy of prematurity (ROP), ocular toxocariasis, and rarely, uveitis and incontinentia pigmenti should be considered in the differential diagnosis.
- In particular, it is important to differentiate severe posterior PFV presenting as bilateral closed-funnel retinal detachment from the Norrie disease. Norrie disease is more hemorrhagic and vascular lesions are more prominent. It occurs in boys and has a very poor prognosis. Genetic analysis is the best way for differentiation. Table 30.1 shows the key clinical features for differential diagnosis.

Natural Course of the Disease

The natural course of untreated PFV is often ill-fated due to the changing nature of the process, resulting in sequelae and complications [1, 16, 25]. Exception to this is mildly affected incomplete forms, for example, when only a small patch of fetal

Table 30.1 Key differentiating features of persistent fetal vasculature and simulating disorders

PFV	• Dx within weeks of birth • Unilateral (90%), mostly sporadic • Microphthalmos, microcornea • Prominent iris vessels, posterior synechia, ectropion uvea, shallow AC, elongated ciliary processes, ACG, cataract, retrolental fibrovascular membrane, stalk emanating from the disc (often with TRD) • RD is tractional and often tent-shaped where the peripheral retina is attached (seldom funnel-shaped RD). Fibrotic attachment to the back of the lens more at the nasal side • Retrolental vessels are typically oriented in a radial pattern, and may anastomose with other vasculature in the iris, ciliary body, or circumlental space
Retinoblastoma	• Dx within months/years of birth (average: 1.5 y of age) • Sporadic (90%) or familial (AD inheritance, 10%) • Unilateral (60%) or bilateral (40%) • Normal-sized eye and cornea (may have buphthalmos) • May have white, fluffy seeds on the iris or in the AC (pseudohypopyon), no cataract • NVI is common and the most frequent reason of secondary glaucoma • RD is exudative with subretinal fluid and seeds • Calcification on ultrasonography and CT scan • FA shows dilated and tortuous vessels diving into the RD and feed the hyperfluorescent tumor • MRI: Iso/hyperintense mass in T1, hypointense mass in T2 sections. Pinealoma may may also be present
Norrie disease	• Dx within weeks of birth • Bilateral, X-linked recessive inheritance, male • Mostly associated with progressive hearing loss and mental retardation • Microphthalmos, iris atrophy and synechiae, shallow AC • Severely dysplastic retina (often with severe subretinal hemorrhage and lipid) • RD is often hemorrhagic and vascular lesions more prominent than PFV • Confirmation by molecular genetic testing
ROP (Stage 4 or 5)	• Dx at birth/within weeks of birth • History of prematurity/low birth weight/neonatal oxygen therapy • Bilateral, may be asymmetric • Normal-sized eye (may have microphthalmos) • Elongated ciliary processes, pupillary membrane and TVL may be seen; however, vascular pattern is more irregular than the radially-oriented retrolental vasculature in PFV • Straightening of the vascular arcades with macular and optic disc dragging is typical • RD is generally tractional with a concave configuration, "peripheral trough" (fold between vascular-avascular retina) is characteristic in stage 5 and leads to funnel-shaped RD
FEVR	• Dx within years of birth (average: 6 years) • Mostly AD inheritance (Examination of asymptomatic family members is helpful) • Bilateral and often asymmetric • Normal-sized eye and cornea

(continued)

Table 30.1 (continued)

	• Peripheral avascular retina, straightening of the vascular arcades with macular and optic disc dragging (ROP-like appearance but slower progression), with or without retinal folds (falciform retinal folds extending mostly to the temporal periphery to the back of the lens), as well as pre-, intra-, or subretinal exudation • RD is typically tractional, but may subsequently develop exudative and/or rhegmatogenous components • FA is essential for accurate dx—peripheral nonperfusion, vessel straightening and anastomoses, telangiectasias and neovascularization are typical
Coats' disease	• Dx at 5–10 y of age • Unilateral (90%), male (80%), sporadic • Normal-sized eye and cornea (may have buphthalmos) • Pupillary reflex is more yellow than white (xanthocoria) • Subretinal lipid exudates with telangiectatic retinal blood vessels • RD is typically exudative
Toxocariasis	• Dx at childhood (usually > 3 years) • History of exposure to puppies, eating dirt • Unilateral • Normal-sized eye and cornea • Granuloma with a stalk can be mistaken for a fibrovascular stalk. However, there is often a significant component of posterior uveitis
PFV persistent fetal vasculature; *Dx* diagnosis; *AC* anterior chamber; *ACG* angle-closure glaucoma; *RD* retinal detachment; *TRD* tractional retinal detachment; *AD* autosomal dominant; *NVI neovascularization of iris; CT computed tomography; FA fluorescein angiography; ROP retinopathy of prematurity; FEVR familial exudative vitreoretinopathy*	

tissue is found on the posterior lens surface as an isolated finding, it may follow a relatively benign natural course and may never require a surgical intervention [1, 2, 29]. However, the vast majority of PFV eyes appear to undergo secondary changes, which may eventually lead to loss of the eye (Figs. 30.8 and 30.9). Reese expressed this as " I have never seen, a single case of uncomplicated full-blown persistent hyperplastic vitreous in an adult, and neither have any of my colleagues" [1].

Clinical observations and pathology findings in the early literature have expanded our understanding of progressive changes in untreated PFV eyes [1, 16]. We know that the fibrovascular plaque undergoes progressive contracture. This contracture likely causes a break in the posterior capsule, thereby causing

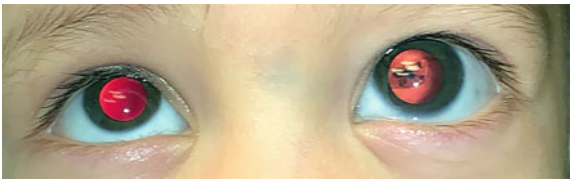

Fig. 30.9 Left eye has mixed PFV with secondary glaucoma causing buphthalmos in an infant

cataractous changes in the lens. This is accompanied by a swelling of the lens, which often comes forward together with the iris and touches the cornea, causing angle-closure glaucoma, corneal edema, scarring and opacification (Fig. 30.8) [1, 2, 6, 16, 25]. Only rarely, instead of swelling, the lens may absorb, partially or totally, and harbor capsular remains. Or it may shrink to a small, white, calcified lesion. These eyes may avoid secondary glaucoma and corneal changes [1]. The progressive contraction of the plaque also exerts constant traction on the ciliary body, which may lead to intraocular hemorrhage, ciliary body detachment, hypotonia, and eventually loss of the eye [1, 2, 6, 16, 25]. Surgery allows us to remove these tractional forces and gives us a chance to change this ill-fated course of the disease.

Treatment

A broad spectrum of presentation translates into a similarly broad range of treatment options and outcomes. At one end of the spectrum, an eye may have only minor sequelae from the fetal vascular structures such as a Bergmeister's papilla (persistent epipapillary fibrovascular tissue), a Mittendorf dot (small retrolental opacity caused by the anterior termination of the hyaloid artery), or persistent pupillary loops and strands. Such eyes, which are minimally affected, with normal visual function or clear visual axis, and without progressive anatomical changes such as shallowing of the anterior chamber or retinal traction, follow an uncomplicated course and remain stable without surgery. Surgery may also be avoided for those at the other end of the spectrum of severity, particularly when PFV is associated with systemic syndromes, such as trisomy 13, or Walker-Warburg syndrome, and the globe is extremely microphthalmic, undifferentiated, and disorganized. Yet for the majority of the PFV cases, surgery is the only treatment option.

- PFV surgery addresses two main problems: One is the media opacities that need to be cleared to prevent amblyopia, and the other is the tractional forces that need to be released to prevent secondary complications such as retinal detachment, glaucoma, ciliary body detachment and phthisis. Because the hyaloidal stalk remains rigid in the growing eye, it exerts anterior, posterior, and circumferential traction on the retina, lens and ciliary body, causing such complications. By releasing the connections of the hyaloid stalk to these structures and clearing the axis, the eye has a chance to grow and achieve acceptable anatomy and function [17, 21, 23, 30, 31].
- In mild to moderate cases, the goal of surgery is to restore vision as much as possible. In severe cases, the primary goal is to salvage the eye and achieve as good cosmesis as possible (Figs. 30.8 and 30.17) and then, if possible, restore some vision. Visual gain is also limited by the degree of retinal dysplasia and optic nerve hypoplasia. To maximize the visual potential, it is essential to coordinate with a pediatric ophthalmologist and combine early surgery with early and aggressive management of amblyopia. The importance of visual

rehabilitation after surgery should be also clearly explained to parents because surgical technique alone will not result in full visual potential without appropriate postoperative rehabilitation.
- One should not forget that these are only spare eyes not normal eyes.

The treatment of PFV was extremely conservative in the early years with the primary aim being the prevention of complications and anatomical preservation of the globe. Although vitrectomy was used in the 1980s, the visual expectations were very limited and severe cases, especially posterior ones have been deemed inoperable for a long time. However, advancements in surgical instruments and technology and greater awareness and understanding of PFV among ophthalmologists over the last decade have changed the disease course. Now, visual gain after surgery is not uncommon for many cases. Reported rates of useful vision (20/400 or better) after surgery ranges from 18 to 79% according to the literature [15, 17, 21–24, 31]. Eyes with anterior PFV, in particular, benefit most from surgery and have been generally associated with more favorable outcomes, when managed properly. In a series of 81 eyes, Sisk et al. [23] reported that 96% of the anterior PFV eyes having undergone surgery achieved counting fingers or better vision at the final follow-up, versus 55% of those with the posterior disease. Similarly, our group reported that 37% of the anterior PFV cases had a final visual acuity of 20/200 or better, and 79% achieved counting fingers or better, whereas respectively 7% and 60% of the cases with posterior involvement achieved the same [15].

Although surgical outcomes in posterior disease still appear somewhat limited, more data has supported the concept of retinal plasticity, even in severe cases. Bosjolie and Ferrone [24] suggested that surgical intervention for posterior PFV eyes up to 1 year of age provided significant reversal of retinal dragging and folds and improvement of visual acuity. The authors emphasized the importance of early intervention before fibrotic retinal changes occur. Walsh et al. investigated the prognosis of bilateral, more severe type mixed PFV eyes. In their study of 22 eyes, 69% maintained at least light perception vision in at least 1 eye, and no more than 11% ended up with phthisis bulbi [30]. The authors advocated surgery in eyes with severe posterior cases who would have likely had poor visual and anatomical outcomes.

Recently, our group have delved into the full spectrum of posterior PFV and investigated outcomes of surgical intervention according to the disease severity, including the ones at the most severe end of the spectrum [18]. In the first group of eyes presenting with typical tent-shaped retinal detachment, the results were comparable to the results of the previous literature, with 90% of the eyes achieving complete or near-complete retinal reattachment and 70% obtaining counting fingers or better vision. Similar to Walsh et al. [30], functional outcomes were limited to light perception vision at best in severe forms of this group who had optic nerve/macula pathologies or severe retinal dysplasia. However, surgery assured a cosmetically acceptable, formed globe in most of them, and only 7% became phthisical. The second group consisted of eyes presenting with leukocoria and closed funnel-shaped RD, which deemed inoperable to date and natural history

inevitably leads to secondary complications and loss of the eye [18]. Surgery restored light perception in 45%; this meant that 70% of patients with bilateral pathology had light perception in at least one eye. Even more importantly, anatomical preservation of the globe was possible in most cases; only 14% resulted in phthisis bulbi, and one required enucleation. These results show that even when a postoperative improvement in visual function is not expected in severe cases, removal of tractions via surgery may allow the relieved retina to settle down over time, prevent hypotony and phthisis, decrease the leukocoric appearance and may even enable some light perception (Fig. 30.8).

PFV Surgery: General Considerations

PFV surgery broadly includes vitrectomy with transection of the persistent hyaloid stalk, with or without lensectomy, and the release of tractions on the ciliary body and the retina by excision of the retrolental tissue and removal of epiretinal membranes. Due to the clinical heterogeneity among PFV cases, each case also brings unique challenges that should be addressed. Before moving on to discuss surgical approaches in different clinical scenarios, the following paragraphs focus on key points for a successful PFV surgery:

1. **Make sure the parents have realistic expectations before surgery**
   Parents of children with vitreoretinal diseases such as PFV often find it difficult to accept that their child may experience permanent vision impairment as a result of the disease. They may perceive the surgery as a miraculous solution and might be eager to proceed. Taking time to discuss the goals, risks, and benefits of surgery, the necessity of postoperative rehabilitation, and set realistic expectations is as important as the surgery. The surgeon should explain the natural course of the untreated disease and the expected benefit-risk ratio of the surgery, but should not promise the outcomes.
2. **Examine the ora serrata-pars plicata area for anatomical variations before placing sclerotomies and use limbal entries until safe**
   The surgeon should be aware that peripheral retinal anomalies are quite common in eyes with PFV, particularly in the anterior form of the disease. The peripheral retina may be dragged anteriorly, replace the pars plana in some parts, and elongate as finger-like extensions; or sometimes it may circumferentially extend beyond the ora serrata and become continuous with the retrolental tissue (Figs. 30.10, 30.11 and 30.12, see **Video** 4). We have previously documented that more than 80% of the anterior PFV cases [15], and up to 27% of the posterior cases [18] with tent-shaped retinal detachment had this anomaly. Therefore, once the child is under anesthesia, a thorough examination is crucial before beginning the surgery. If there is an extensive fibrovascular membrane obscuring the view, it would be safer to use limbal entries for the entire

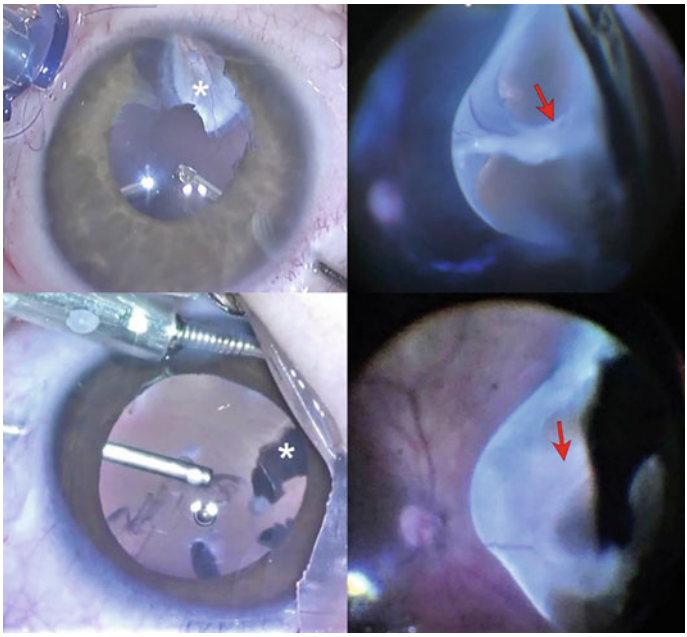

Fig. 30.10 Examples of elongated peripheral retina parts (arrows) that insert into the ciliary processes or more anteriorly, into the retrolental plaques (*)

procedure or until an adequate view of the peripheral retina is achieved. Some clues may also guide the surgeon to detect areas of retinal elongation; nasal and inferiorly localized pigmented or fibrovascular plaques are the places where elongated retina parts are most commonly found (Fig. 30.10).

3. **Always prioritize complete removal of retrolental fibrovascular tissue rather than preservation of the capsule to avoid potential complications**
   Rare cases with localized avascular plaque located centrally behind the lens, leaving the peripheral parts of the lens clearer, may allow safe removal of the entire lens opacity while preserving the peripheral capsule for a secondary intraocular lens implantation. However, in cases with extensive and eccentric fibrovascular tissue, complete removal of this tissue should be targeted, as residual fibrovascular tissue contracts over time, leading to pupillary obliteration, angle-closure glaucoma, and chronic peripheral TRD (Fig. 30.11).
4. **Check for the possible continuity of the fibrovascular tissue with the retina before attempting complete removal and be prepared in advance**
   As essential as it is to completely remove the fibrovascular tissue, the surgeon should not rush through it. First, the central portion of the fibrovascular tissue should be sufficiently cleared to examine the peripheral retina (Figs. 30.1g and 30.13). If there is an extensive anterior retinal elongation, the possibility of leaving a thin circle of the peripheral fibrovascular tissue remnant which is

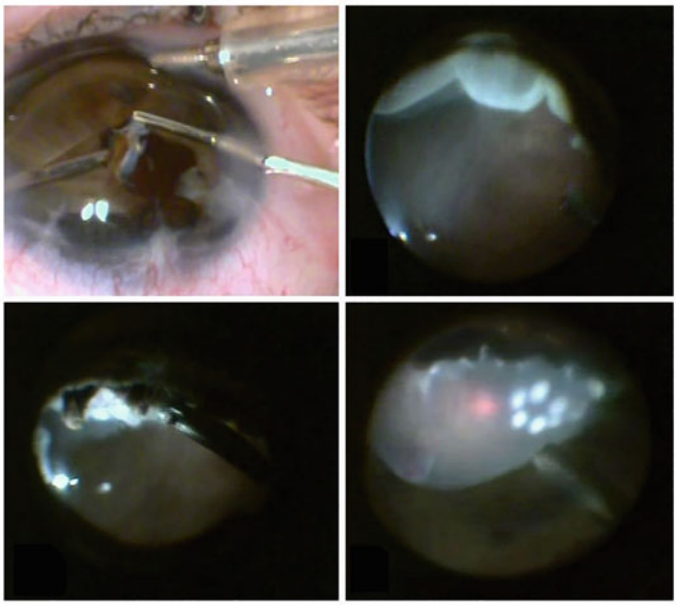

Fig. 30.11 An 8-month-old infant with anterior PFV who had previously undergone lensectomy followed by several operations for pupillary obliteration; There was iris neovascularization and the pupillary aperture was obliterated by a thick and tenacious membrane that was hard to separate. Peripheral retina was detached. The pupillary membrane was continuous with the detached retina in some parts, causing traction. Removal of residual fibrous membranes, 360° retinotomy, photocoagulation and silicone oil tamponade resulted in retinal reattachment

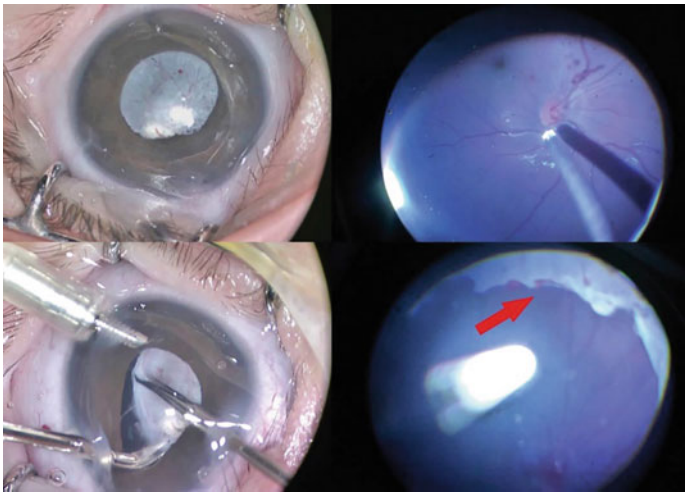

Fig. 30.12 Anterior PFV case in which the peripheral retina was continuous with the anterior fibrovascular tissue. Cutting the fibrovascular tissue resulted in an iatrogenic retinotomy (arrow). In this case, posterior hyaloid was separated, 360° laser photocoagulation and silicone tamponade were applied

segmented with multiple radial incisions should be weight against total removal of that tissue which ends up with retinotomy. When total removal leading to retinotomy is planned, the posterior hyaloid should be separated first to get prepared for retinal breaks before clearing the entire fibrovascular tissue-capsule complex. Otherwise, posterior hyaloid separation may be extremely difficult once an extensive retinotomy has occurred (Figs. 30.12 and 30.14).

5. **Carefully examine the hyaloid stalk for the presence of retinal tissue or vessels**
   The surgeon should be aware that the retinal tissue and vessels may be pulled up and dragged onto the stalk tissue. To avoid rhegmatogenous complications, it is crucial to examine the stalk before transecting it. Aside from direct examination, pushing the stalk from side to side and observing how this alters the retinal circulation can be used as a guide to understand whether or not there are vessels in the stalk. If this occurs, the stalk can be left longer to be on the safe side. There is no need to remove the entire stalk since both ends of the stalk regress postoperatively.
6. **Plan for a staged surgery rather than risking the eye with a retinal break in case of closed funnel RD in eyes with severe mixed PFV**
   In these eyes, surgery starts with limbal entry and lensectomy. Retrolental membranes are dissected starting from the center, layer by layer, to reach the retina as it is done for stage 5 ROP to open the funnel (Fig. 30.17). It is often not possible to completely flatten the retina in such cases of closed funnel posterior PFV. The goal is to dissect the membranes and release tractional forces to allow the retina to gradually go backwards and flatten over time. The surgeon should always remain on the safe side during dissections, as a single retinal break often renders the pediatric eye inoperable. A second surgery may be planned for further membrane dissection 3-6 months later when the retina settles down and go backwards as in stage 5 ROP.

Clinical Scenarios and Surgical Strategies

Case Presentation 1. Mild Anterior PFV

A 2-year-old boy presented for a routine ophthalmological examination. He was born full term by normal vaginal delivery and otherwise healthy. The family history was unremarkable. He was able to fix and follow objects with both eyes. Ocular examination revealed a posterior polar cataract and a retrolental fibrous tissue located nasally at the periphery of the lens capsule in the left eye (Fig. 30.13). A thin hyaloid remnant was observed extending nasally from the optic nerve head and attaching to the retrolental plaque (Fig. 30.13b). There was no microphthalmia. Examination of the right eye was normal. A diagnosis of unilateral mild anterior PFV was made and she underwent lensectomy-vitrectomy surgery. In this case,

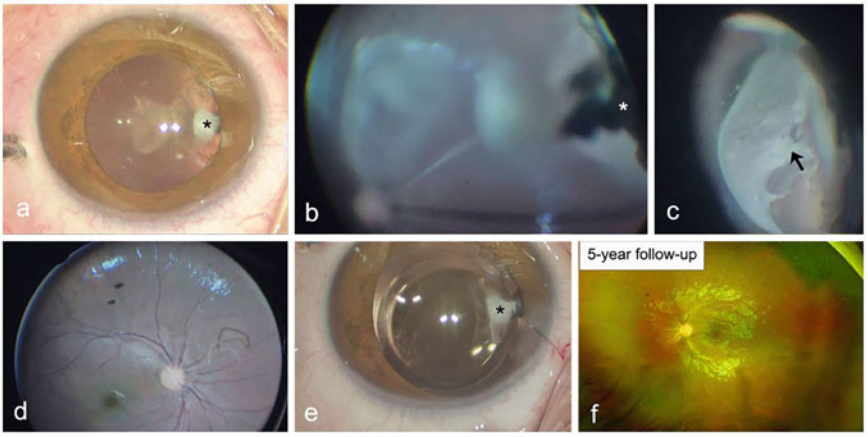

Fig. 30.13 Ocular findings of Case 1 at surgery and at 5-year postoperative follow-up. Note the avascular plaque (*) that had been left in place and mild peripheral retinal elongations (arrow) located in that area

although there was a central opacity of the lens, the retrolental fibrous plaque was small, avascular and attached to the nasal paracentral lens. Although the peripheral retina adjacent to the fibrous plaque had some thin projections anteriorly; none of them was a broad connection (Fig. 30.13c). Because the avascular plaque did not carry a risk for future contraction, it was left in place, the peripheral capsule could be preserved and an IOL was implanted at the time of surgery (Fig. 30.13e). After 5 years of follow-up, visual acuity was 20/50. Visual axis remained clear without secondary proliferation of the residual membrane. Retina was completely attached as seen on the color fundus image (Fig. 30.13f).

Case Presentation 2. Severe Anterior PFV

A 2-month-old boy presented with unilateral leukocoria. He was born full term by normal vaginal delivery and otherwise healthy. The family history was unremarkable. He did not respond to light stimulus in the left eye. Ocular examination showed microphthalmia, retrolental fibrovascular membrane, and a typical radial iris vessel (Fig. 30.14). The pupillary dilation was poor due to posterior synechia. The posterior segment view was obscured and there was a very thin hyaloid artery connection which was barely visualized on ultrasonography (Fig. 30.14b). Examination of the right eye was normal. A diagnosis of unilateral severe anterior PFV was made and he underwent vitreoretinal surgery. Limbal entries were made. Adequate pupillary aperture was achieved with synechiolysis and insertion of the iris retractors. Vascularized, dense, fibrous tissue with elongated and centrally dragged ciliary processes are seen in the image (Fig. 30.14c). The fibrovascular plaque was opened centrally in the first stage and the peripheral part was left in

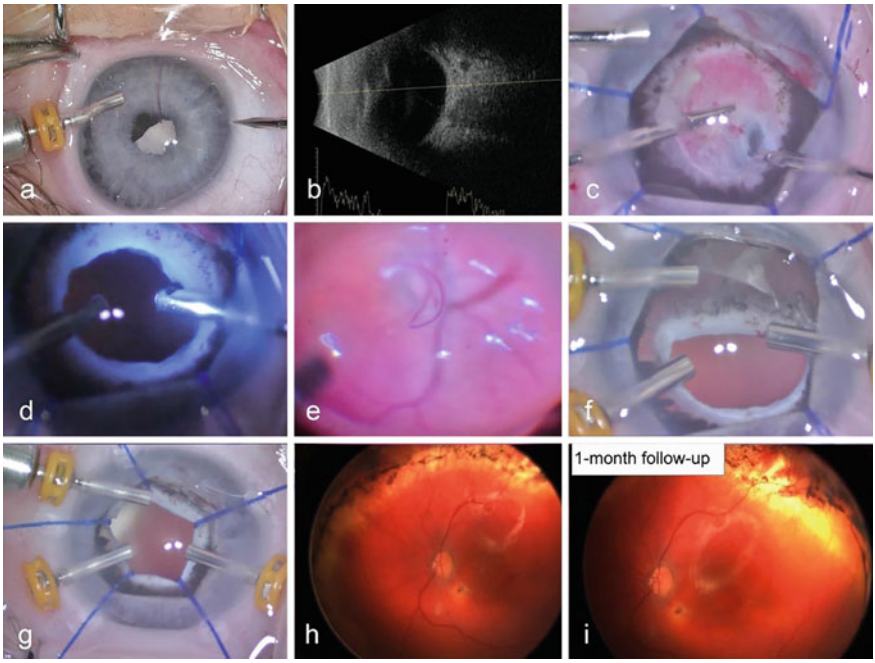

Fig. 30.14 Ocular findings of case 2 during surgery and at early postoperative follow-up

place in case there was a peripheral retinal anomaly (Fig. 30.14d). Retina was attached and there was a thin hyaloid artery connection (Fig. 30.4e). However, since a 360° peripheral retinal extension and direct continuity of the retina with the fibrovascular plaque were detected, preparations were made for a 360° retinotomy by separating the posterior hyaloid first. At this point, the ciliary body and retina, which are the continuation of the ring-shaped fibrovascular tissue remnant, were dramatically detached just before the retinotomy was made (Fig. 30.14f) and the operation could only be continued by holding this tissue with the iris retractors (Fig. 30.14g). Retinal detachment surgery was terminated with 360° retinotomy and silicone tamponade (Fig. 30.14h). At postoperative 1 month, the retina was attached with 360° laser retinotomy margins (Fig. 30.14i). However, this eye was lost to become phthisic because of hypotonia.

Case Presentation 3. Anterior PFV Presenting with a Pseudo-Hyaloidal Stalk [20]

2-month-old boy was referred for bilateral congenital cataracts. He was born full term via normal spontaneous delivery. Systemic evaluation yielded no associated systemic anomalies. The family history was remarkable for an older sibling who had bilateral congenital cataracts, clinical and surgical details of which were not known. Ocular examination revealed near-total white cataract with only a thin rim

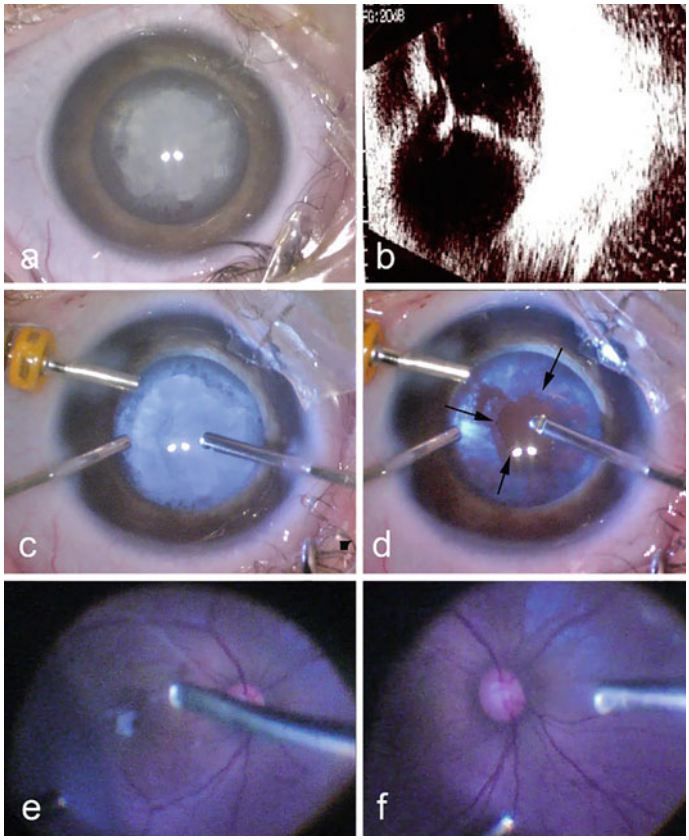

Fig. 30.15 Surgical findings of Case 3 presenting with pseudo-hyaloidal stalk

of clear zone at periphery in both eyes (Fig. 30.15a). There was no fibrovascular structure visible within or behind the lens. The corneas were of equal and normal size, and no associated microphthalmia was present. B-scan ultrasonography showed a hyperechoic band extending from the optic nerve head to the posteriorly-bulged back surface of the lens in each eye, representing a persistent hyaloidal stalk and leading to the diagnosis of bilateral anterior PFV (Fig. 30.15b). Cataractous lens was noticed to be located relatively posteriorly, in the anterior vitreous, at surgery (Fig. 30.15c). During lensectomy, lens particles were noticed to be moving anteriorly from central mid-vitreous towards the aspiration port and the central part of posterior capsule was observed to be developmentally- defective with accompanying white dots (Fig. 30.15d). Lens particles along the Cloquet's canal were removed during central core vitrectomy (Fig. 30.15e). Retina was attached and the optic disc was totally normal even without any stalk (Fig. 30.15f). The peripheral capsule was preserved for future IOL implantation. Both eyes were fitted with contact lenses in the postoperative period and followed up for 2 years. The

patient had secondary proliferation of the capsular epithelium blocking the visual axis in the right eye within 4 months and required a second surgery. Visual acuity was central steady maintained in both eyes at final exam.

Case Presentation 4. Posterior PFV with Tent-Shaped TRD

A 14-month-old female infant presented with strabismus in the right eye for several months. She was born full term by normal vaginal delivery and otherwise healthy. The family history was unremarkable. She had esotropia and responded to light stimulus without fix and follow reaction in the right eye. She was able to fix and follow objects with the left eye. Ocular examination revealed microphthalmia and a hyaloid remnant extending between the back of the lens (narrow attachment seen as mittendorf dot, Fig. 30.16a) and the retina (causing peripapillary tent-like retinal detachment, Fig. 30.16b, c). Examination of the left eye was normal. A diagnosis of unilateral posterior PFV was made and she underwent lens-sparing vitrectomy and patching of the left eye for amblyopia treatment. After 8 years of follow-up, visual axis remained clear with a very small opacity at the back of the lens and the acuity was 20/100. Color fundus and optical coherence tomography images show complete flattening of the retina with residual fibrosis at the optic nerve head (Fig. 30.16d).

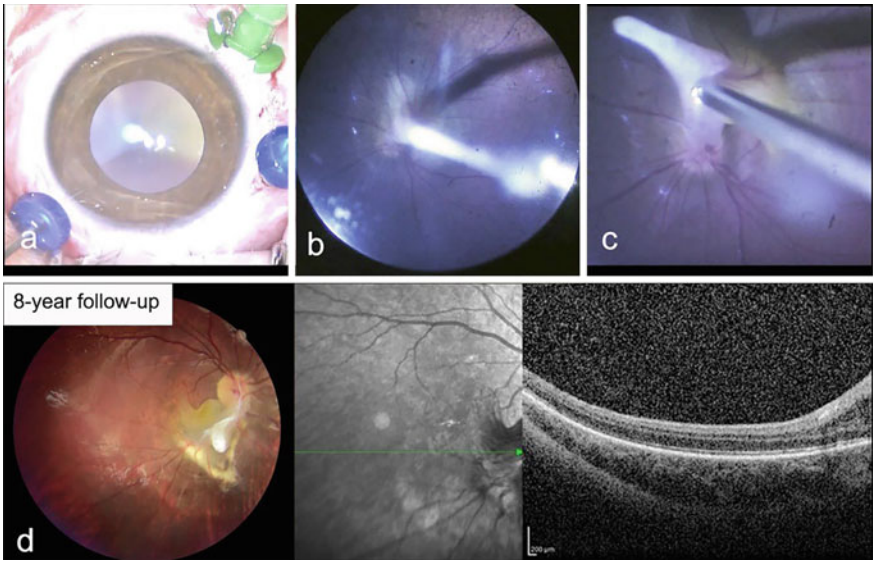

Fig. 30.16 Ocular findings of Case 4 at surgery and at 8-year postoperative follow-up

Case Presentation 5. Severe Mixed PFV with Closed Funnel-Shaped TRD

A 3-month-old boy was referred with the suspicion of bilateral retinoblastoma. The family had noticed white pupils in both eyes a month ago. He was born full term by normal vaginal delivery and otherwise healthy. The family history was unremarkable. He did not respond to light stimulus in either eye. Ocular examination showed microphthalmia, microcornea with corneal diameters of 9 mm, and leukocoria in both eyes (Fig. 30.17a). The posterior segment view was totally obscured. There was no sign of a mass in orbital MRI. Ultrasonography revealed closed funnel-shaped retinal detachment in both eyes. A diagnosis of bilateral severe mixed PFV was made and he underwent limbal lensectomy-vitrectomy. Although retina was severely dysplastic, wide opening of the funnel was possible with meticulous dissection of retrolental and preretinal membranes in both eyes (Fig. 30.17b–e). Retina was partially attached in the posterior pole at 6-month follow-up and light perception vision was achieved in both eyes (Fig. 30.17f).

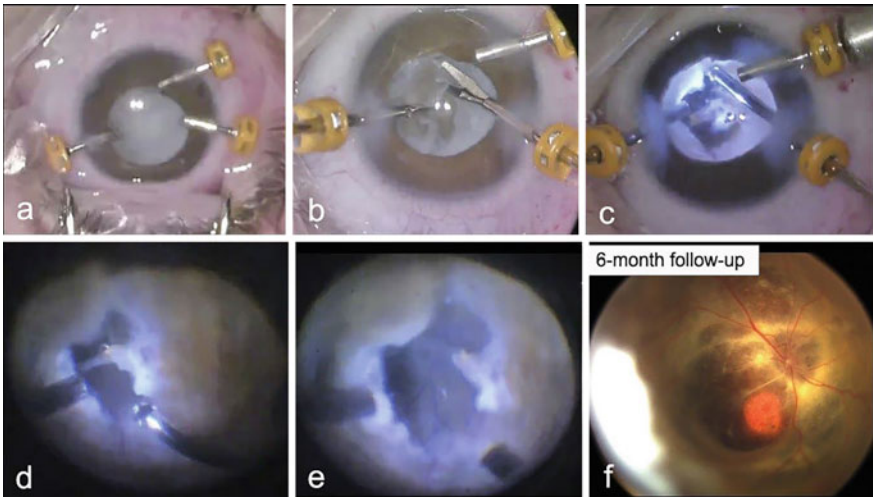

Fig. 30.17 Ocular findings of Case 5 at surgery and at 6-month postoperative follow-up

Conclusions

PFV represents a broad spectrum of anomalies and presentations, which translates into a wide variety of potential outcomes. In general, purely anterior PFV cases have better visual potential than those with posterior malformations; however, many cases with posterior PFV may also achieve useful vision with proper care.

Severe cases may benefit from surgery in terms of anatomic preservation. Peripheral retinal anomalies are much more common than previously thought. Keeping this in mind, extra care should be taken to avoid complications in cases that might otherwise have good visual and anatomical outcomes. All in all, prognosis depends on the severity and type of the disease as well as early diagnosis and intervention, careful planning of the surgical technique, frequent follow-ups, family education and postoperative management of amblyopia.

Review Questions

1. Which of the following statements is true about PFV?

a. Consanguinity is a significant risk factor for the disease development.
b. A meticulous systemic work-up is crucial following the diagnosis of PFV.
c. Ultrasonography and direct visualization are usually enough for PFV diagnosis.
d. Most of the cases remain stable throughout life without surgery.

2. Peripheral retinal anomalies and anterior elongations are most commonly seen in which type of PFV?

a. Predominantly anterior PFV
b. Predominantly posterior PFV
c. Mixed PFV
d. b and c

3. Which of the following statements is true about PFV?

a. Peripheral remnant of retrolental fibrovascular tissue can be left in place and serve as a bed for secondary IOL implantation.
b. Severe mixed type PFV with closed-funnel shaped TRD often presents with bilateral involvement.
c. The growth of the microphthalmic globe to normal dimensions after the operation is an indicator of surgical success.
d. It is necessary to remove the entire hyaloid stalk to prevent its later contraction.

Answers

1. **(C)** Although autosomal dominant or recessive inheritance has been reported in very few cases, PFV is mostly a sporadic non-heritable disease. PFV typically presents without associated systemic findings and routine systemic work-up is not required. Diagnosis of the disease is based on ocular examination and visualization of fetal vascular remnants. Except for the very mild forms, the majority of PFV cases undergo progressive anatomic changes and end up with secondary glaucoma, corneal opacification, and eventual phthisis bulbi.

2. **(A)** Peripheral retinal anomalies are quite common in eyes with PFV, particularly in the anterior form of the disease reaching up to 80% of the cases [15]. It is crucial to check for possible anomalies before placing sclerotomies or to use limbal entries until safe. The nasal and inferior quadrants adjacent to localized pigmented or fibrovascular plaques are the most common sites where retinal elongations are detected.

3. **(B)** Retrolental fibrovascular tissue should be completely removed as residual tissue contracts over time, causing pupillary obliteration, angle-closure glaucoma, and chronic peripheral TRD. Mixed anterior–posterior PFV with closed funnel-shaped TRD is a rare form of PFV and often presents with bilateral involvement (2/3 of this form in our practice). Enlargement of the microphthalmic globe to normal size should alert the physician to the possible development of glaucoma. It is often sufficient to transect the stalk to release antero-posterior traction. The surgeon can shorten the stalk it as long as it is safe. As retinal tissue and vessels are often dragged up to the stalk tissue, attempting a complete removal is very risky and often not possible.

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