

# Late sequelae of retinopathy of prematurity in adolescence and adulthood

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## Abstract:

This article provides information about late complications of retinopathy of prematurity (ROP), especially seen in adolescence and adulthood. The majority of ROP patients recover without complications and treatment, but severe ROP cases should be properly treated. Both prematurity itself and the treatment of ROP cause some changes in the anterior (refractive changes, cataract, and glaucoma) and posterior segments (tractional, rhegmatogenous and exudative retinal detachment, vitreous hemorrhage, etc.) of the eye and predispose to significant lifelong complications. Awareness of these late complications can minimize severe vision loss with proper follow-up and appropriate treatment. Therefore, life-long ophthalmological follow-up is mandatory in all prematures with the diagnosis of ROP.

## Keywords:

Adult retinopathy of prematurity, cicatricial retinopathy of prematurity, late sequelae, retinopathy of prematurity

## INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of retina occurring in premature infants. Advances in neonatal care and ROP treatment has led these babies to live longer with this disease. Most of the ROP cases regress without the need for treatment with no complications, but severe ROP cases should be treated properly. Retinal cryoablation, which was used in the treatment of severe ROP in the past, has now been replaced by laser ablation therapy and intravitreal anti-vascular endothelial growth factor (VEGF) injections. ROP with retinal detachment (stage 4 and 5) requires vitreoretinal surgery. All of these therapies as well as prematurity itself have specific anatomical concerns and long-term complications which makes ROP a lifelong disease to be followed routinely. Table 1 the list of long-term complications.

## ANTERIOR SEGMENT COMPLICATIONS OF ADULT RETINOPATHY OF PREMATURETY

The prematurity and low-weight birth, apart from ROP, can be associated with refractive errors,<sup>[1-3]</sup>

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strabismus,<sup>[4-6]</sup> cerebral visual impairment,<sup>[7]</sup> reduced contrast sensitivity,<sup>[8]</sup> visual field defects,<sup>[9]</sup> and decreased visual acuity.<sup>[3,10]</sup>

Premature babies may develop refractive errors due to alterations in the anterior segment, such as a shallow anterior chamber, a steep cornea, or a thick lens, as well as changes in the posterior segment, such as a longer axial length.<sup>[11,12]</sup> Intravitreal Anti-VEGF injections have been shown to cause myopia and astigmatism in ROP patients, however to a lesser extent than laser ablation of the peripheral retina.<sup>[13-15]</sup>

Infants with ROP have shorter axial lengths, shallower anterior chambers, and more highly curved corneas than eyes of premature infants without ROP and full-term infants.<sup>[16]</sup> Angle-closure glaucoma is a known complication in ROP patients and is seen with a frequency of 1%–2%.<sup>[17,18]</sup> The angle become narrower due to choroidal congestion and anterior displacement of the ciliary body, causing forward shift in the iris-lens diaphragm, especially if diode laser treatment or scleral buckle surgery was performed.<sup>[19]</sup> ROP and ROP treatment induces myopia and may cause relative anterior microphthalmus.<sup>[20]</sup> These changes may lead to angle-closure glaucoma in adulthood even in patients with regressed ROP.

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**Table 1: Long-term complications of retinopathy of prematurity**

Anterior segment complications	Posterior segment complications
Highly-curved cornea	Late tractional, rhegmatogenous or exudative retinal detachment
Increased lens thickness	Persistent avascular retina
Cataract	Retinoschisis
Angle-closure glaucoma	Smaller foveal avascular zone and foveal hypoplasia
High myopia	Retinal vascular disorders

The treatment for threshold ROP has been evolving since 1980s. The first results of the CRYO-ROP study in 1988<sup>[21]</sup> and laser ablation therapy in the early 1990s<sup>[22-24]</sup> showed significant success for the treatment of threshold ROP disease. Anterior segment complications such as eyelid swelling, conjunctival hyperemia and corneal clouding were reported after both cryotherapy and laser ablation treatments which are usually temporary.<sup>[25]</sup> The ablation of the retinal tissue through which the long posterior ciliary arteries pass and the compression of the long posterior ciliary arteries during scleral depression may impair blood flow and cause anterior segment ischemia which is a dreaded complication of ablative treatments.<sup>[26]</sup> Hypotony, iris atrophy, corneal edema, and cataract may occur secondary to anterior segment ischemia which may result in phthisis and loss of the eye.

The development of cataract may also be linked to ROP. Davitt *et al.* reported 1.9% of infants with ROP developed cataract.<sup>[27]</sup> Ezisi *et al.* reported an incidence of cataract of 0.97% in patients with ROP.<sup>[28]</sup> Cataract may be associated with prematurity itself, as well as interventions for ROP such as laser photocoagulation, intravitreal anti-VEGF injection, or lens-sparing vitrectomy or cicatricial changes.<sup>[29]</sup>

Severe inflammatory response may occur after cryotherapy/laser ablation, especially with successful heavy ablation therapy. Inflammation may cause iris posterior synechia, lens hydration and cataract development. The thermal effects of the laser may also stimulate cataract formation.<sup>[30]</sup> Punctuated or vacuolated focal opacities can be seen at the capsular or subcapsular level which may spontaneously resolve over a period of 2–6 weeks.<sup>[31]</sup> This complication may be more common in patients with tunica vasculosa lentis because the laser energy can be absorbed more, causing the lens to heat.<sup>[22]</sup> Microperforations in the lens capsule with the laser ablation treatment may also cause a phacoantigenic response leading to cataract formation.<sup>[32]</sup> Cataract is a well-recognized complication following vitrectomy which may develop in 5.6%–19% of the cases.<sup>[33-37]</sup> Mean time between vitrectomy and lensectomy was reported to be between 7 and 21 months.<sup>[33-36]</sup> Cataract can develop as a result of lens-retina apposition, lens touch during surgery, or chemical alterations caused by the vitreous surgery or the tamponade agents used.<sup>[34]</sup> One of the main differences of the pediatric lens is that, a small lens trauma caused by lens touch during vitreoretinal surgery

may form a small scar and stay localized without progressing for a long time in contrast to the adult cases. That is why the lens may still be spared during vitrectomy if the lens touch is small and paracentral.<sup>[35]</sup>

Krolicki and Tasman reported that cataract surgery in adults with cicatricial ROP may increase visual acuity and ease glaucoma management.<sup>[38]</sup> Improvement in visual acuity after cataract surgery is limited by retinal findings. Kaiser *et al.*<sup>[39]</sup> reported that, 56% of the adult patients with a history of ROP had minimal cicatricial changes and 23% of them had postoperative retinal tears or detachments. They stated that cataract surgery required close retinal follow-up even in ROP patients without any retinal changes.

There is also an increased risk of anterior segment complications during surgery because of the zonular weakness.<sup>[28]</sup> Cicatricial membranes may reach to the back of the lens and may cause progressive subluxation of the lens capsule and intraocular lens postoperatively [Figure 1].

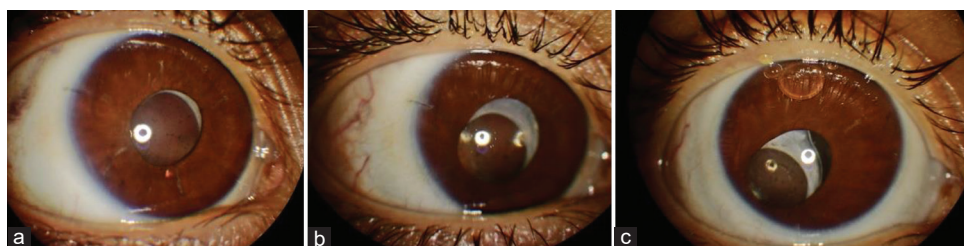
## POSTERIOR SEGMENT COMPLICATIONS OF ADULT RETINOPATHY OF PREMATUREITY

Most cases of ROP will regress whether with treatment or spontaneously. Several factors including zone and stage of the ROP, the type of treatment applied, and the timing of the treatment may affect long-term sequelae. The third edition of International Classification of ROP (ICROP-3) described the long-term sequelae features of regressed ROP which are rhegmatogenous/tractional/exudative retinal detachment, retinoschisis, peripheral avascular retina which is prone to peripheral retinal degenerations and tears, macular anomalies and retinal vascular changes.<sup>[40]</sup>

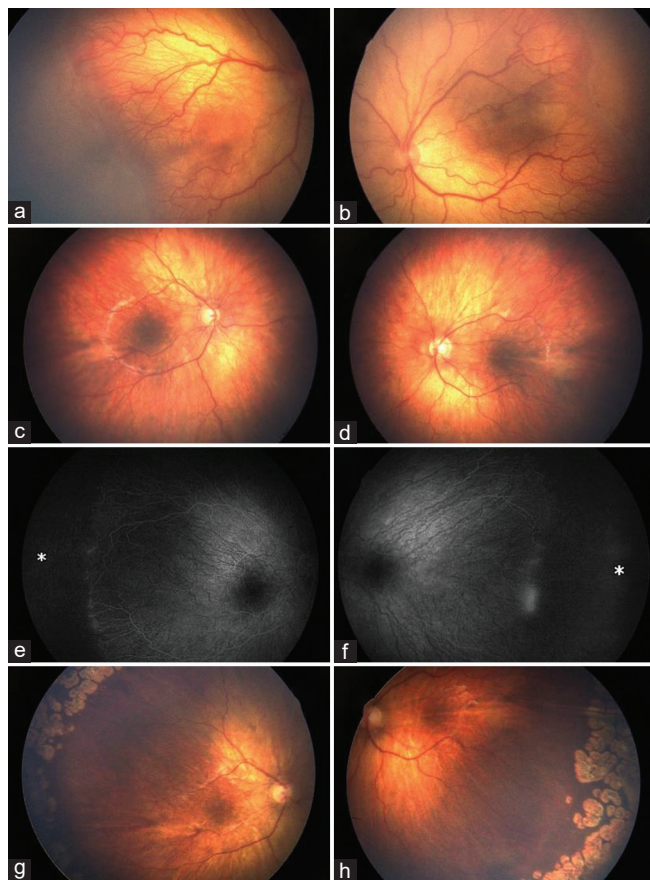
## PERSISTENT AVASCULAR RETINA

Over the past 10 years, the mainstay of Aggressive ROP (A-ROP) treatment has shifted from laser photocoagulation to intravitreal anti-VEGF injection. Anti-VEGF injection therapy has superiority over laser ablation therapy in long-term especially for anterior segment and refractive aspects.<sup>[41]</sup> However, recurrence of ROP and the need of extended follow-up due to incomplete retinal vascularization are the main disadvantages of intravitreal anti-VEGF treatment as compared to laser ablation [Figure 2].<sup>[42]</sup> Anti-VEGF agents for ROP treatment have been demonstrated to end up with abnormal vascular structures and avascular areas in the peripheral retina in recent fluorescein angiography (FA) studies. Persistent peripheral avascular retina (PPAR) has been reported to be present in 44%–100% of eyes treated with intravitreal anti-VEGF agents after 45-week post-menstrual age.<sup>[14,43-49]</sup> Active retinal neovascularization, vascular leakage, and abnormal vascular structures may be seen in 23.5%–40% of the cases with PPAR.<sup>[14,45,46]</sup>

Late-onset exudation and fibrovascular proliferation may rarely occur in adolescents and adults previously treated with bevacizumab for ROP.<sup>[50-52]</sup> After anti-VEGF injections,



**Figure 1:** An 11-year-old girl with cicatricial retinopathy of prematurity presented with rhegmatogenous retinal detachment and cataract in the right eye. Pars plana vitrectomy combined with cataract surgery was performed to the right eye (a). Although retinal reattachment was maintained, but a progressive post-operative intraocular lens-capsular bag subluxation developed due to zonule weakness and secondary cicatricial changes during 12 months follow up period (b and c)



**Figure 2:** A 7-year-old girl born at the 22+5 weeks gestation with a birth weight of 542 grams who had been treated with bilateral intravitreal aflibercept injection for Aggressive retinopathy of prematurity (A-ROP) at post-menstrual age 37 weeks (a,b). A-ROP was regressed after treatment, but retinal vascularization was interrupted and progressed slowly. Bilateral macular was normal (c,d) on examination under general anaesthesia performed at the age of 10 months, but fluorescein angiography revealed avascular Zone 2 (marked with asterisk), abnormal branching anastomosing peripheral vessels in right eye (e) and avascular Zone 2 (marked with asterisk), finger like peripheral vessels, leakage in left eye (f). Bilateral laser ablation was performed to the avascular retina at the same time with the examination (g,h)

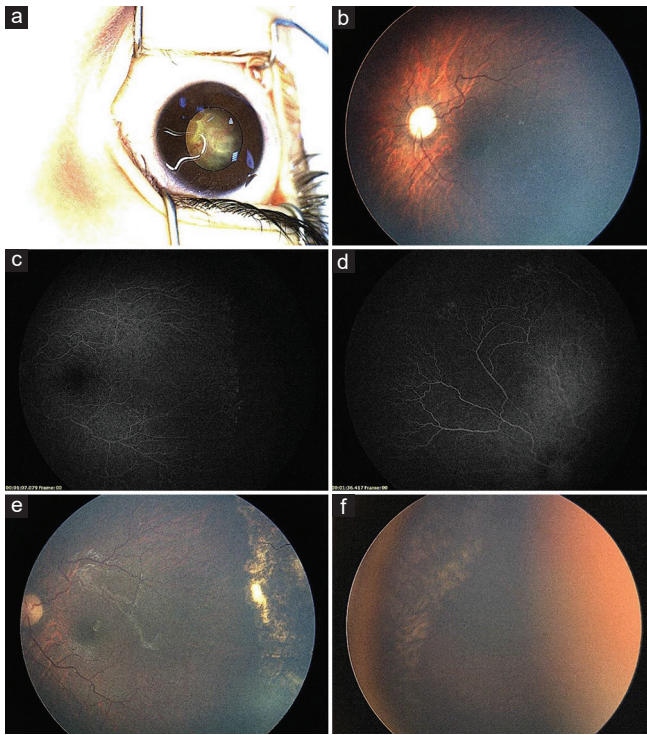
long-term close follow-up is critical until retinal vessels reach 2-3 disc diameters from the ora serrata to prevent late-onset reactivation due to PPAR.<sup>[53]</sup> FA is a good tool to follow for the late onset reactivation of ROP.

PPAR is known to be thinner than the normal vascularized retina. This thinned, avascular tissue may develop atrophic retinal holes, lattice degeneration, and retinal tears. Since there are several vitreoretinal interface pathologies in these areas in ROP survivors, atrophic holes and lattice degeneration may easily progress to rhegmatogenous retinal detachment (RRD).<sup>[54]</sup> Close follow-up with FA and laser ablation of PPAR is recommended to treat late reactivation and prevent progression to RRD.<sup>[50]</sup> Laser ablation is unquestionable when there is leakage due to neovascularization in the ridge on FA. However, there is still debate on laser treatment for PPAR without leakage. Most authors recommend laser photocoagulation if there is still PPAR in zone 1 or 2 by 50-60 weeks of PMA.<sup>[55]</sup> Delaying of the laser therapy has some advantages and drawbacks. Advantage of delaying laser ablation with strict follow-up may allow retinal vascularization to progress and enable to perform laser photocoagulation to less area of avascular retina which may also decrease late refractive complications. However, delaying the laser treatment may increase the risk of retinal complications like late reactivation of the disease, retinal tear, and detachment [Figure 3].<sup>[50,56,57]</sup> The peripheral retinal examination would be very difficult after 60 weeks of PMA because of the growing baby who is becoming stronger and harder to stabilize for the examination. That is why we usually do FA at 60 weeks PMA and do laser if there is still PPAR to prevent later retinal complications.

### RETINAL DETACHMENT

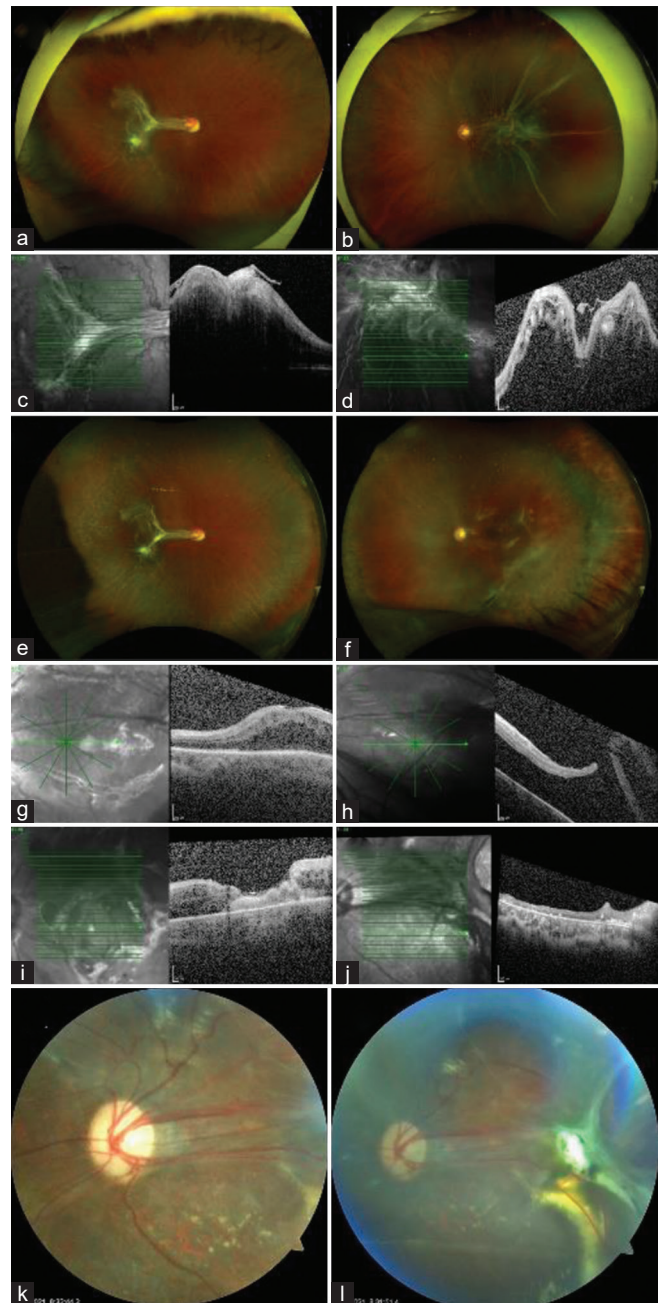
All types of RD; RRD,<sup>[58-60]</sup> tractional (TRD)<sup>[58,59,61]</sup> or exudative (ERD)<sup>[62,63]</sup> RD may occur as a long-term complication of ROP. The most common type of RD are RRD or combined rhegmatogenous and tractional retinal detachments. Hamad *et al.* reported that only 13.6% of eyes in their cohort had purely TRD.<sup>[54]</sup> TRD is more common in early ages like 2-4 years of age, and RRD is more common after 6 years of age.<sup>[59,64]</sup> ERD is the least common type and usually occurs later in life like the third decade.<sup>[62]</sup>

Contributing factors to RRDs included atrophic holes within peripheral avascular retina, visible vitreous condensation ridge-like interface with residual traction, and premature vitreous syneresis.<sup>[35]</sup> The role of the vitreous in the development of late RRD in ROP has been previously



**Figure 3:** A 3-year old girl who was born with a gestational age of 30 weeks and a birth weight of 600 grams was referred to our clinic with the diagnosis of leukocoria in the right eye when her mother noticed strabismus (a). She had not been screened for retinopathy of prematurity (ROP) during infancy. Examination under general anaesthesia showed total retinal detachment in the right eye (A) and normal looking fundus in the left eye (b). FA revealed peripheral avascular retina in the left eye (c,d). The patient was diagnosed as stage 5 ROP in the right eye and persistent avascular retina due to regressed ROP in the left eye. Surgery was not suggested for the right eye but laser ablation was performed to the left eye to prevent late complications (e,f)

recognized. Posterior hyaloid is tightly adherent to the ridge in ROP cases. Premature vitreous liquefaction occurs especially in eyes with neovascular activity.<sup>[65]</sup> Partially liquefied vitreous and syneresis lead to early posterior vitreous detachment. Retinal breaks that occurred after posterior vitreous detachment may develop at the ridge location in adulthood. However, most of the retinal tears causing RRD are not associated with a posterior vitreous detachment, especially in patients with persistent avascular retina who have thinner retina with firmly attached vitreous [Figure 4]. Eye growth and progressive retinal stretching in areas near the less elastic ridge-like tissue interface caused by regressed fibrovascular ridge tissue, as well as age-related vitreous condensation or contraction, could be a cause of these tears.<sup>[54]</sup> Two large retrospective studies which included a population primarily born before the CRYO-ROP, reported long-term complications of ROP. Kaiser *et al.* reported an RD rate of 14.6% and retinal tear rate of 10.6%.<sup>[66]</sup> Smith and Tasman reported an RD rate of 25.6%, with a mean age of onset of 35 years (14–51 years).<sup>[67]</sup> In a multicenter retrospective study on long-term retinal complications in untreated ROP, a retinal tear rate of 31%, atrophic holes rate of 35% and retinal detachments rate of 39% were reported in ROP survivors with



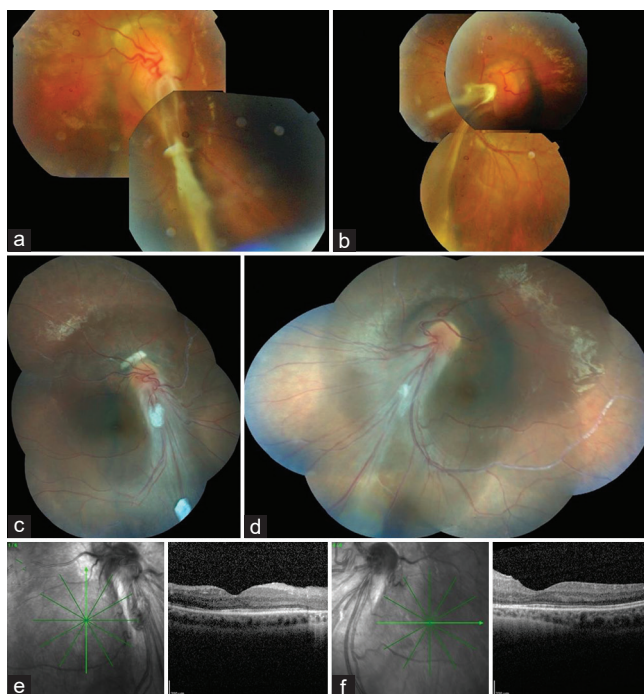
**Figure 4:** A 12-year-old male patient was born at the 32 weeks of gestational age and a birth weight of 2000 grams. He had a history of hospitalization in neonatal intensive care unit for two months. He did not have treatment for retinopathy of prematurity as an infant and was referred with sudden vision loss in the left eye. His visual acuity was 20/400 OD and counting fingers (CF) at 1 meter OS. Examination at baseline revealed bilateral macular dragging secondary to fibrotic membranes at the fovea and peripheral avascular retina (a-d). Rhegmatogenous retinal detachment caused by retinal break at the upper temporal quadrant was present in the left eye (b, d). Combined scleral buckle and vitrectomy was performed to the left eye and prophylactic laser photocoagulation was performed to the pigmented lattice degenerations in the avascular retina in the right eye to prevent retinal breaks (e,f). Retina was attached at post-operative 1st month (g) but repeat vitrectomy needed due to recurrent retinal detachment caused by a secondary macular hole (h). Amniotic membrane graft was placed on the macular hole (i) and closure of the macular hole was provided (j). Anatomical success was achieved after the third surgery, but the vision remained at CF at 1 meter (k,l)

a mean age of 34.5 years.<sup>[35]</sup> We believe that laser ablation of the peripheral retina may decrease the risk of future retinal break and hole formation which further helps to decrease the risk of RRD.

The surgical treatment of late RRD may involve vitrectomy, scleral buckle, or combined surgery. Scleral buckle is an ideal treatment for isolated RRD in adult ROP patients if retinal break (s) can easily be identified preoperatively and are located in mid-zone 2 or anterior zones. Zone 1 or posterior zone 2 breaks and those associated with tractional membranes may need to be treated with vitrectomy or combined vitrectomy-buckle procedures. The prognosis is guarded with significantly lower success rates than the other adult RRDs. Park *et al.* reported 20% anatomical success rate in patients aged 2–15 years.<sup>[58,66,68,69]</sup> and they stated that visual prognoses of these patients are poorer than those with late retinal detachments that occur in adult ROP patients.<sup>[54,58,60,66,68,69]</sup> Scleral buckling procedures had better success rates than vitrectomy or combined procedures.<sup>[54,60]</sup> Tufail *et al.* reported single surgery success rate of 73% with scleral buckle in ROP patients with late RRD compared to 57% with vitrectomy.<sup>[60]</sup> Hamad *et al.* reported that primary success rate was 64% with scleral buckle and 36% with vitrectomy or combined procedures in such cases. Hamad *et al.* also noted that 36% needed two or more surgeries.<sup>[54]</sup>

TRD may occur as a sequelae of cicatricial ROP and can be explained by proliferation and contraction of tissue originating in the ridge area.<sup>[69]</sup> We want to emphasize that fibrotic tissue causing traction is not elastic and becomes even tighter with time and with growth of the eye, which may lead to gradual increase in traction causing TRD and even RRD within months to years.<sup>[61]</sup> Although the prognosis is guarded with relatively poor anatomical and functional success rates, it has a better outcome than RRD or combined detachment cases in general.<sup>[59,61]</sup> Machemer described five cases of TRD that developed later in life as a result of cicatricial ROP.<sup>[69]</sup> He reported that all patients achieved an increase in visual acuity with vitreous surgery, which had previously been slowly decreasing.<sup>[69]</sup> Park *et al.* reported that anatomical success rate was 54.5% in TRD group which was higher as compared to 20% in the RRD group.<sup>[59]</sup> Visual prognosis was even worse. Our group have reported anatomical and functional results of vitreoretinal surgery in 11 eyes of 10 patients with TRD associated with late cicatricial ROP [Figure 5].<sup>[61]</sup> We have reported 91% anatomical success rate and improvement in visual acuity in 82% of the cases with TRD in cicatricial ROP patients who have never been treated during infancy for ROP. In addition, 27% of eyes had a final visual acuity of 20/200 or better.<sup>[61]</sup> We assume that relatively higher success rate can be explained with careful selection of patients for surgery. Those eyes with membranes causing an anteroposterior traction rather than tangential traction which look relievable without taking too much risk of retinal break are the best candidates for this surgery [Figures 5 and 6].<sup>[61]</sup>

Late exudation and ERD is a very rare late complication of regressed ROP. The pathogenesis of late ERD is uncertain.

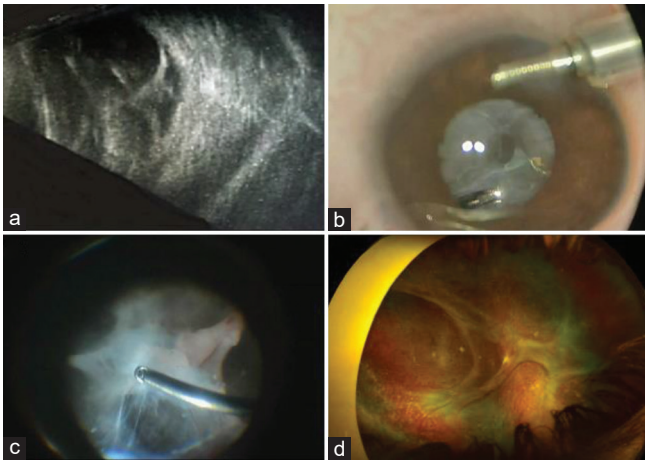


**Figure 5:** A 6-year-old boy born with a gestational age of 28 weeks and a birth weight of 1300 grams who has never been followed or treated for retinopathy of prematurity before was referred to our clinic with bilateral tractional retinal detachment caused by fibrotic membranes extending from optic nerve head to the back of the nasal part of the lens anteriorly and nasal periphery resulting in inferonasal foveal ectopia and detachment (a and b). Visual acuity was 0.15 in the right eye (RE) and 0.1 in the left eye (LE). Lens sparing vitrectomy with air tamponade was performed on both eyes and macula was attached (although displaced inferonasally) (c and d) with a very well-formed foveal contour in optical coherence tomography (e, f). VA was 0.7 in the RE and 0.3 in the LE

Retinal dragging, abnormal telangiectatic vessels, and vasoproliferative tumors have been reported in patients with late exudative RD.<sup>[62,63]</sup> The late reactivation may also be likely due to persistent avascular retina producing constant low levels of VEGF. Therefore, close follow-up and ablation of peripheral avascular retina should be considered in patients with ROP, regardless of treatment history, to decrease lifelong risk of severe complications, including retinal detachment decades later.<sup>[70]</sup> It is also important to differentiate ERD from familial exudative vitreoretinopathy when we see exudative findings by ordering a genetic test and doing a family screening.

## VITREOUS HEMORRHAGE

Although trauma is the most common cause of vitreous hemorrhage in children, regressed ROP was reported to be the most common cause of non-traumatic spontaneous vitreous hemorrhage in children.<sup>[71]</sup> AlHarkan reported that 20% of vitreous hemorrhage was caused by regressed ROP in children between 1 and 5 years of age.<sup>[72]</sup> Vitreous hemorrhage is a poor prognostic sign in active high-risk ROP, but not in regressed ROP.<sup>[73]</sup> Vitreous hemorrhage may occur as a result of abnormal



**Figure 6:** A 4-year-old boy was born at the 28 weeks of gestational age and with a birth weight of 1000 grams and presented with bilateral leukocoria. His visual acuity was hand motions in the right eye (RE) and no light perception in the left eye (LE). It was learned from his history that he was diagnosed as bilateral stage 5 retinopathy of prematurity in the first examination when he was discharged from the neonatal intensive care unit. There was leukocoria in the RE and corneal opacification and very shallow anterior chamber associated with leukocoria in the LE. B-scan ultrasonography revealed vitreous membranes causing anteroposterior tractional retinal detachment (TRD) in the RE (a) and closed funnel retinal detachment in the LE. Surgery was not suggested to the LE but a lensectomy-vitreotomy was performed for the RE. Per-operative picture after partial dissection of the membranes show that there was TRD associated with retinal folds and some limited areas of attached retina (stage 4b) (b and c). Postoperative anterior segment and fundus pictures at 2 years. Retinal folds settled down with larger areas of attached retina (d) after vitrectomy with lensectomy and his visual acuity increased to 20/400 with aphakia correction

vitreoretinal traction disrupting normal retinal vessels or bleeding on cicatricial tissue by vitreous traction. Early vitrectomy is advocated in ROP patients with vitreous hemorrhage since RRD may also accompany the vitreous hemorrhage.<sup>[74]</sup>

## FOVEAL HYPOPLASIA/SMALLER FOVEAL AVASCULAR ZONE

Foveal formation begins in the 22<sup>nd</sup> week of GA, foveal depression appears between the 24<sup>th</sup> and 28<sup>th</sup> weeks, and foveal maturation continues until the age of 4 years.<sup>[75]</sup> ROP has been linked to abnormal foveal development such as absence or swallowing of foveal pit, persistence of inner retinal layers in the center, macular edema, increased foveal thickness and delayed photoreceptor development for a long time.<sup>[76,77]</sup> Takagi *et al.* reported the foveal avascular zone is smaller in children with a history of ROP compared to children who were not premature.<sup>[78]</sup> Akula *et al.* reported that increasing ROP severity (term, none, mild, severe) was associated with decreased visual acuity and foveal depth.<sup>[79]</sup> Sukgen *et al.* evaluated that there may be a relevance between foveal hypoplasia and PPAR.<sup>[49]</sup> This finding could indicate that foveal development may be linked to peripheral retinal vascularization.

## CONCLUSION

All patients diagnosed with ROP at neonatal age, whether treated or regressed spontaneously, should be followed for life-long and evaluated for possible anterior or posterior segment changes that may affect visual acuity. We recommend routine follow-up in these patients to prevent, detect, and treat complications as early as possible.

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## Conflicts of interest

There are no conflicts of interest.

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