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REVIEW

New insights in diagnosis and treatment for Retinopathy of Prematurity

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Abstract The purpose of this study was to review current perspectives on diagnosis and treatment of Retinopathy of Prematurity (ROP). We performed a systematic review of how much has been produced in research published online and on print regarding ROP in different settings around the world. Early Treatment for ROP (ETROP) classification is the currently accepted classification of ROP. Fluorescein angiography and spectral domain optical coherence tomography (SD-OCT) may eventually lead to changes in the definition of ROP, and as a consequence, they will serve as a guide for treatment. Intravitreal anti-VEGF therapy has proven to be more effective in terms of lowering recurrence, allowing growth of the peripheral retina, and diminishing the incidence of retinal detachment when proliferative ROP is diagnosed. Whether anti-VEGF plus laser are better than any of these therapies separately remains a subject of discussion. Telemedicine is evolving everyday to allow access to remote areas that do not count with a retina specialist for treatment. A management algorithm is proposed according to our reference center experience. ROP is an evolving subject, with a vulnerable population of study that, once treated with good results, leads to a reduction in visual disability and in consequence, in a lifetime improvement.

Keywords Retinopathy of prematurity · Angiography · Tomography · Algorithm · Guidelines · Bevacizumab · Aflibercept · Ranibizumab · Vitrectomy · Telemedicine · Laser

Introduction

In 1984, the International Classification of Retinopathy of Prematurity (ICROP) was published and since then it has been the guideline for the diagnosis of retinopathy of prematurity (ROP), with a valuable update on July 2005 [1]. With the advent of spectral domain optical coherence tomography (SD-OCT) as a portable tool (iVue) [2] available for use in infants, and the widespread use of fluorescein angiography (FA) in vascular diseases of children, this classification must be eventually modified according to new findings described by different research groups.

The location of retinal involvement, extent by clock hours, stage of severity, and the presence of plus disease, are still considered as the main features for classification.

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This article intends to inform the readers what has advanced in the diagnosis, treatment, and follow-up of ROP, not to propose a new classification.

Location and extent of disease

In order to classify the disease, the retina has been divided in Zone I, II, and III. Zone I represents a circle with a radius that extends from the optic disk to twice the distance from the center of the optic disk and the central macula. Zone II starts from the edge of zone I to the nasal ora serrata. Zone III is the residual temporal retina anterior to zone II. Disease extension is reported as clock hours [1].

Stages

ROP is classified in five stages where the union of vascular and avascular retina plays a major role. The observer rates the disease according to the most severe manifestation observed. FA findings are reported by clinical stage. At our center, we perform FA in selected patients with ROP, especially those with stage 2 or more, because it has proven to make a more accurate diagnosis, avoiding subjective grading differences [3–5].

Fluorescein angiography (FA)

Being a complex and incompletely understood process, vasculogenesis is being better studied with FA. Several particular characteristics for grading ROP are observed and described as follows:

Fluorescein Angiography by stages

Stage 1

Hyperfluorescent flat demarcation line between vascular and avascular retina, formed by capillaries, with mild fluorescein leakage from the vascular wall [6].

Stage 2

Hyperfluorescent elevated demarcation line (ridge) with mild fluorescein leakage due to vascular incompetence, and some visible tufts or "popcorn" lesions [6] (Fig. 1).

Stage 3

Marked leakage at the ridge, where neovascularization or a fibrovascular proliferation into the vitreous is observed [6].

Stage 4 and Stage 5

There are no specific FA findings. Leakage is observed where neovascularization is present. The clinical picture is characteristic (stage 4a partial retinal detachment without macular involvement, stage 4b partial "macula-off" retinal detachment, and stage 5 with total retinal detachment) [1].

Peculiar characteristics are observed in cases with aggressive posterior retinopathy of prematurity (AP-ROP), where capillary closure that indicates nonperfusion, marked vessel tortuosity, shunts, leakage from the neovascular tissue, and tufts are observed [7].

Treatment follow-up with FA

With FA, progression of retinal vasculature towards the periphery has been documented after intravitreal bevacizumab treatment [7] (Fig. 2).

New insights with FA

As FA allows the practitioner not only to grade the disease but also to distinguish variations on presentation, we have made several observations in older and heavier children that are classically described as having ROP, even though their gestational age is beyond the limit of pathological vasculogenesis with high oxygen concentrations. Instead, we hypothesize that they may be just affected by high doses of oxygen [9]. This must be extensively studied.

Optical coherence tomography

Spectral domain optical coherence tomography (SD-OCT) is currently being used by some centers, to identify different morphological characteristics of the globe in children with ROP. We use the iVue SD-OCT system (Optovue Co, Fremont, CA), which is a hand-held device with an axial resolution of

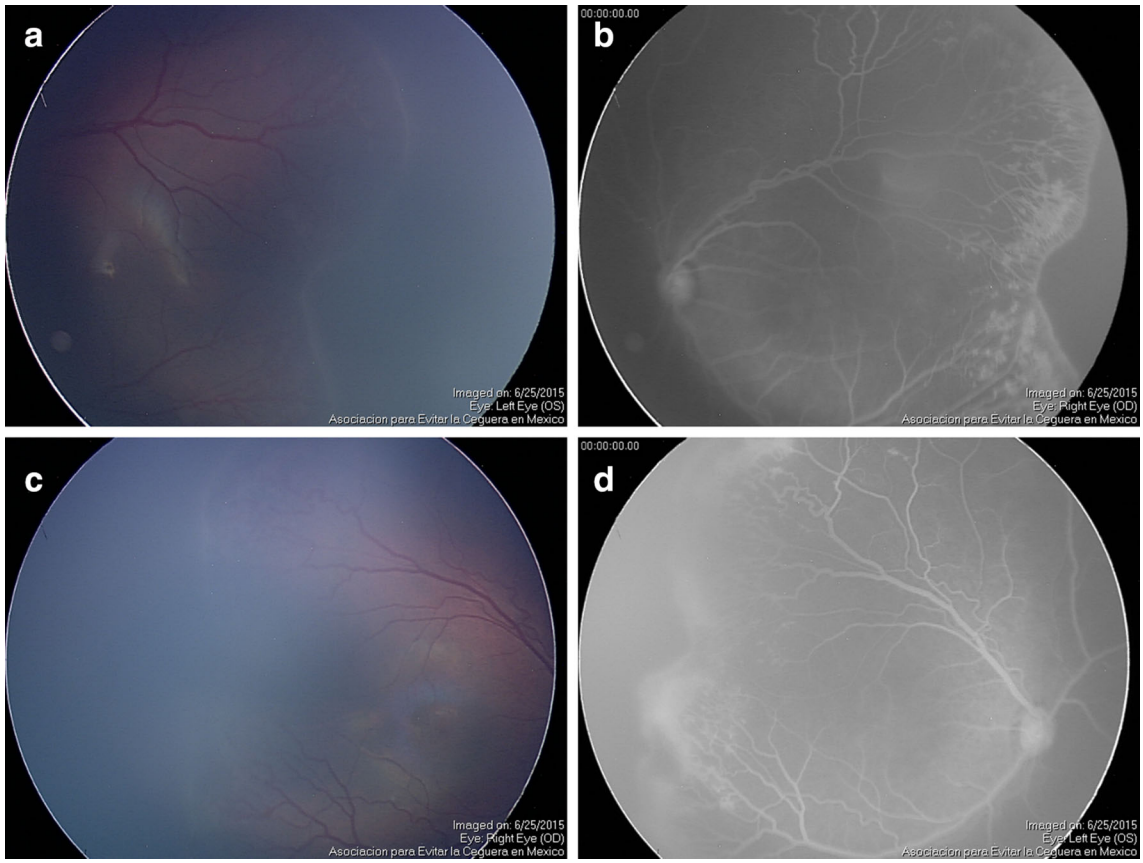

Fig. 1 Differences observed at the demarcation line using fluorescein angiography. **a** *Left* eye. Clinically observed ROP in Zone I, Stage 2. **b** *Left* eye. FA with no leakage, according to clinical diagnosis. **c** *Right* eye of the same patient with ROP Zone I Stage 2. **d** Corresponds to its FA with dye leakage from neovascularization at the ridge, according to Stage 3

5 microns that performs 26,000 scans per second with an 840-nm laser of superluminescent diode [2], which results very convenient because of its portability, allowing to perform studies in children confined to a hospital bed. SD-OCT has been validated with the correlation between images and histologic specimens at the fovea. It can be used to observe the iridocorneal angle, the fovea, the ridge, and fibrovascular proliferations [10, 11].

SD-OCT for the evaluation of the macula

Vinekar et al. [12] made an important report of macular findings correlated with visual acuity in children diagnosed with ROP with a clinically "normal-looking" fovea. Macular edema was detected by SD-OCT in 29.1 % of the patients with stage 2 ROP before the 52nd week of postmenstrual age (third corrected month). Visual acuity was worse in the eyes with macular edema compared to the control groups. However, this difference was statistically significant up to the 3rd month and not thereafter [12–14]. Morphology of the edema was sub-classified in two patterns: pattern A, a dome-shaped elevation in the center of the fovea with intraretinal cysts, vertical septae, and complete disruption of the foveal depression; pattern B: multiple confluent hyporeflective spaces within the layers of the retina without septae and a preserved foveal depression. Macular edema has been hypothesized to be related to high concentrations of vascular endothelial growth factor (VEGF) [15].

SD-OCT can also demonstrate the disrupted retina when tractioned (Fig. 3), as well as serving to demonstrate choroidal changes indicating that the retina is thinner in threshold ROP than in patients with a history of ROP and spontaneous regression [15].

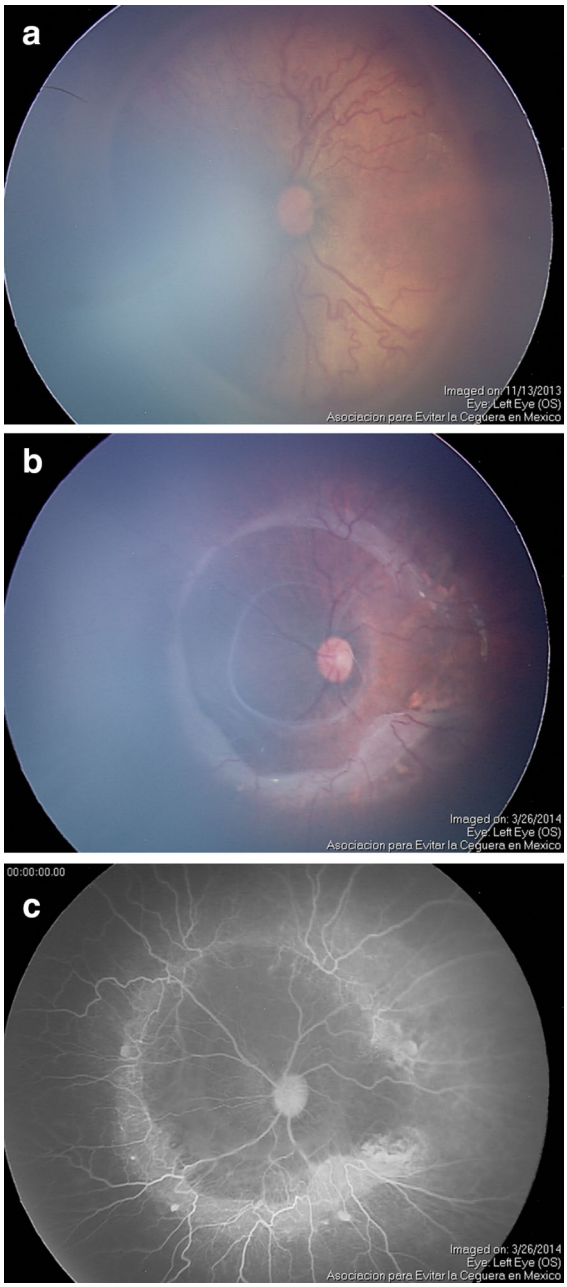

Fig. 2 Growth beyond the demarcation line observed after Intravitreal bevacizumab. **a** Corresponds to a *left* eye with Stage 4a with plus disease. **b** Same eye 19 weeks after treatment with intravitreal bevacizumab (IVB). **c** corresponds to the FA 19 weeks after treatment with IVB, the vessels have passed beyond the demarcation line towards the periphery

Erol et al. [16] showed a patient whose cystoid macular edema resolved two months after treatment with intravitreal bevacizumab (IVB); this supports the

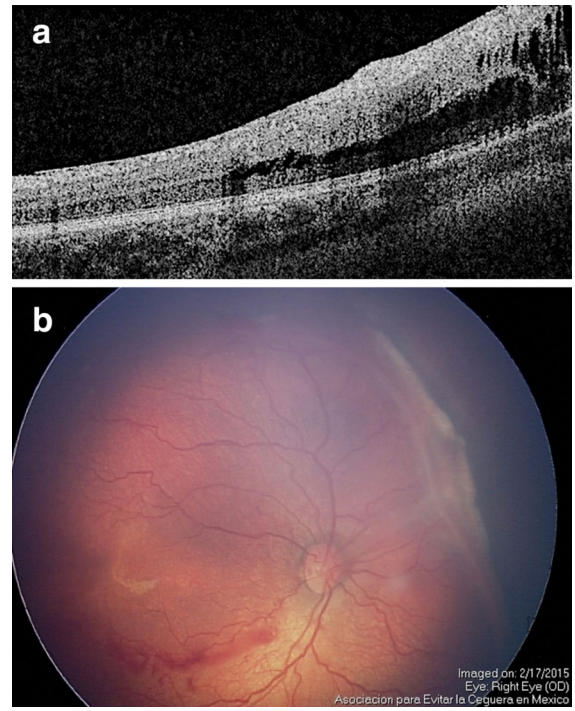

Fig. 3 Use of optical coherence tomography in ROP. Optical coherence tomography **a** of the ridge of a ROP stage 4a **b** that shows traction and cystic degeneration secondary to it

fact that VEGF is a mediator factor involved in its pathogenesis.

SD-OCT for follow-up after treatment

SD-OCT is a valuable tool for follow-up of patients, either treated or untreated, since it can display differences with growth or at different gestational ages. Comparing SD-OCT with FA could be very valuable to support theories about cystoid macular edema in preterm newborns. It is known and reported that preterm infants do not have a foveal avascular zone formed, while its relation to the presence of cystoid macular edema is still unknown [8].

Treatment

At different time points, several studies have produced answers that lead to better therapeutic options. The first one, the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) not only established the definition of *threshold* disease (defined

as at least 5 contiguous or 8 cumulative sectors or clock hours of stage 3 ROP in zone I or II in the presence of plus disease), but also the effectiveness of cryotherapy for severe ROP in an attempt to destroy the cells that produce VEGF in the retina. Despite its efforts, only a 50 % reduction of evolving to retina detachment was obtained; regarding visual acuity at 10 years, only 45.5 % achieved 20/40 or better [17, 18]. Later, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) showed that supplemental oxygen therapy for prethreshold disease did not offer any significant benefit. Also, the Light Reduction in Retinopathy of Prematurity Cooperative Group (LIGHT-ROP) demonstrated a lack of response when light exposure was reduced to newborns from birth to 32 weeks of postmenstrual age [19, 20].

It was not until the Early Treatment for Retinopathy of Prematurity (ETROP) [21] results were published that the term *Prethreshold* ROP was defined as any ROP in zone I that was less than threshold, or in zone II stage 2 with plus disease, or zone II stage 3 disease without plus disease, or zone II stage 3 with plus disease but fewer than five contiguous or eight cumulative clock hours. Also, this study group indicated that peripheral retinal ablation should be considered for any eye with

Type 1 ROP:

1. Zone I, any stage ROP with plus disease or
2. Zone I, stage 3, with or without plus disease or
3. Zone II, stage 2 or 3 ROP, with plus disease

The same publication indicates that continued examination before peripheral retinal ablation should be considered for

Type 2 ROP:

1. Zone I, stage 1 or 2 with no plus disease or
2. Zone II, stage 3 with no plus disease

Treatment must be considered if a type 2 ROP progresses to type 1 or there is a threshold ROP appearance. When management was initiated in high-risk prethreshold eyes, there was a better structural and visual outcome [22].

Although this classification has resulted really useful, it is based on clinical findings that may vary between clinicians. In order to establish the need for treatment, FA has resulted especially useful since it usually reveals zones of stage 3 disease that may be missed clinically, therefore tilting the scale to favor treatment in eyes that clinically do not fulfill ETROP criteria [21, 22].

Laser

In the 1980 and 1990s, treatment of stage 3 + disease underwent a slow transition from cryotherapy to laser therapy. Both of these treatments destroy the majority of the cells that produce VEGF in the retina [17, 22].

Laser photocoagulation is the gold standard treatment for proliferative ROP. Laser treatment has proven useful to reduce progression of ROP. However, disease progression requiring retreatment occurs in approximately 11–20 % of eyes despite peripheral ablation [23]. Also, there are several pitfalls with the use of laser ablation, such as permanent reduction of the visual field, induction of myopia, reduced night vision, and impaired dark adaptation. These are the reasons why some clinicians are shifting their treatment preference towards the use of anti-VEGF agents [24, 25].

Intravitreal anti-VEGF treatment

In a controlled, multicenter clinical trial (BEAT-ROP: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity), reported that in infants with zone I stage 3 + disease, the recurrence rate with intravitreal bevacizumab was 4 %, compared with 22 % with laser therapy alone [23]. Some advocate for monotherapy with anti-VEGF medications to allow growth to the retinal vasculature beyond the demarcation line. Other authors such as Kim et al. [26] consider that treatment with bevacizumab plus laser treatment for ROP type 1 in zone 1 is more effective: they followed patients treated with a combination of laser and bevacizumab for 41 weeks, and neither recurrence nor retinal detachment was found in the 18 eyes studied. Either ranibizumab or bevacizumab or aflibercept is being used for treatment [27–29].

Systemic side effects are still of particular interest, as preterm infants with proliferative ROP have a compromised blood-retinal barrier possibly allowing a large amount of VEGF inhibitors to enter the bloodstream [30]. Infants with ROP may still be in the process of organogenesis, in which VEGF still plays an essential role [23]. In the only randomized study by Mintz-Hittner, five infants died in the bevacizumab group compared to two infants in the laser photocoagulation group [23]. The five patients receiving

intravitreal bevacizumab died of asphyxia (two infants, 16.3 and 12.3 weeks after intravitreal injection of bevacizumab or IVB), respiratory failure (two infants, 4.8 and 13 weeks after IVB), and adherence to do-not-resuscitate order (one infant, 0.4 weeks after IVB). The infants of the control group died of sepsis (one infant, 4.8 weeks after laser photocoagulation) and respiratory failure (one infant, 4.2 weeks after laser photocoagulation) [23]. In our series, we have observed regression of ROP and structural changes associated with intravitreal injections with bevacizumab (IVB) (Avastin; Genentech, Inc., South San Francisco, CA 0.625 mg, 0.025 mL solution) in the retina of children treated according to the ETROP criteria with no side effects directly attributable to the injection (Prethreshold ROP and threshold ROP) [27, 28, 31–33]

We perform fundus FA in patients that fulfill treatment criteria, using 10 % fluorescein administered intravenously as a bolus at a dose of 0.1 mL/kg. Mydriasis is obtained with tropicamide and phenylephrine 2.5 %. Infants are imaged with the RetCam II (Clarity Medical System, Pleasanton, California, USA).

We noted ROP regression after IVB in 15 ± 10.7 days, after initial therapy. The structural changes associated with therapy were a fibrous line at the demarcation line in patients that had plus disease, and posterior vitreous detachment in cases with mild peripheral vitreous traction before treatment [32, 33]. We did not observe any recurrence of ROP in our series treated with bevacizumab [32].

Regarding whether ranibizumab, bevacizumab, or aflibercept is the treatment of choice is still under study. Wong et al. report a 83 % of reactivation using ranibizumab vs none with bevacizumab [34]. On the opposite side, Chen et al. observed that both anti-VEGF showed similar efficacy in the regression of ROP [35].

In our experience, a single dose of IVB has shown to induce ROP regression and seems to be effective and well tolerated, especially in stage 3. IVB allows the growth of retinal vessels across the demarcation line and towards the periphery [36]. Also, VEGF inhibitors may be used as an adjuvant of laser treatment or after vitrectomy to obtain improved outcomes [24].

Surgery

In the past, ROP surgery was performed as an open-sky procedure, or a pars plicata approach with lensectomy. With the advent of new instruments for retinal surgery, approach to ROP is more feasible and yields better results [37].

Vitrectomy has been performed with 20, 23, and 25 gauge [37–43]. Whether a lens-sparing vitrectomy or a vitrectomy/lensectomy surgery must be performed is term of discussion. Lens-sparing vitrectomy diminishes traction in ROP detachments and improves visual rehabilitation by reducing risk of aphakia or by anisometropia by scleral buckling.

Besides, the results of the surgery depend on ROP stage. In a retrospective review, a reattachment rate after lens-sparing vitrectomy was 82.1 % for stage 4a, 69.5 % por stage 4b, and 42.6 % for stage 5 [37]. El-Rayes et al. obtained a retinal reattachment in lens-sparing vitrectomy of 71.8 versus 75 % in lensectomy plus vitrectomy for stage 4b retinopathy of prematurity [44]. Lakhanpal et al. [38] reported that depending on the funnel configuration of stage 5 ROP their results varied with a 20-gauge vitrectomy: the stage 5 with an open anteriorly–open posteriorly configuration of the retinal detachment was, according to them, more amenable to lens-sparing vitrectomy where 57.1 % of patients were anatomically reattached at the final visit; compared to a 25 % of reattachment of eyes with open anteriorly–narrow posteriorly configuration funnel.

In a report of patients with stage 4a or 4b, operated with 20-gauge instruments, only 5.6 % developed cataract and 3.7 % required lensectomy due to impairment of the visual axis [37]. This must be taken into account when final visual acuity is being measured because not only the opacity modifies vision, but also because when a lens-sparing vitrectomy is performed, there is a less induced myopia when compared to eyes treated with laser alone [37, 38, 40].

Anti-VEGF treatment can be also used as a coadjuvant therapy before surgery to reduce vascularization at the moment of surgery [41]. As we mentioned earlier, at our center we have observed that after anti-VEGF therapy, a posterior vitreous detachment occurs on ROP stage 4a that releases traction at the ridge. This mechanism sometimes leads to retinal detachment resolution, thus avoiding surgery.

At our institution, we perform a three-port pars plicata vitrectomy with or without lensectomy depending of lens status in stage 4a, 4b, or 5 (open funnel) with a 25-gauge port 1 mm posterior to the limbus. At stage 4a, we use intravitreal anti-VEGF before the surgery, either ranibizumab (0.25 mg/0.025 mL) or bevacizumab (0.625 mg/0.025 mL). If the patient responds to therapy,

Fig. 4 Management algorithm. We propose the use of the Type 1 and Type 2 ROP for diagnosis according to ETROP. If Type 1 ROP is diagnosed, immediate intravitreal anti-VEGF is injected, and one week later is revised; if more neovascularization is observed by wide angle camera, retreatment must be considered with or without laser; continue weekly observation. Anti-VEGF switch is evaluated if a lack of response initially is observed. Laser is considered for applying to the avascular retina if an aggressive posterior ROP (AP-ROP) is suspected; on the opposite side, if there is regression of neovascularization, weekly observation up to week 52 is opted, then, monthly through the 6th month of life. If AP-ROP is suspected since the first examination, intravitreal bevacizumab is injected. If a stage 2 ROP is diagnosed with clinical image or, if clinical picture is not definite, FA must be realized. In Type 2 ROP, eyes must be re-checked one week later: if it progresses to type 1 ROP, it must be treated accordingly; if ROP regresses, we must check the children up to week 52 and then monthly through the first 6 months of life. In retinal detachment associated to ROP, we perform the following: Stage 4a, we first inject bevacizumab and in less of 48 h we perform vitrectomy if we do not observe improvement (release of traction); in cases of 4b, vitrectomy is immediately performed. Preferably a lens-sparing vitrectomy, depending on lens status. And in the worst prognosis stage of ROP, stage 5, if by echography the retina is detached in an open funnel manner, we can consider as a rescue technique performing vitrectomy and lensectomy plus instant rehabilitation; if the funnel is closed, we only observe and rehabilitate. *NV* neovascularization

tight observation (every 24–48 h) is instituted; if more traction occurs or there is no evidence of response, vitrectomy with or without lensectomy is realized as soon as possible. When facing a stage 4b, if possible, a lens-sparing vitrectomy is performed, again, depending of lens condition. By consensus at our center, when a stage 5 with an open funnel configuration is faced, vitrectomy and lensectomy are both performed. Sole observation and rehabilitation are indicated when a closed funnel stage 5 ROP is diagnosed. We propose a management algorithm for treatment (Fig. 4). Indirect ophthalmoscopy is an alternative when wide-angle camera is not available.

Telemedicine

Digital fundus imaging is now accepted worldwide as a tool for ROP screening. However, the true potential of this technology is being fully exploited now that this method of imaging is used in patients without direct access to a retina specialist or an ophthalmologist with experience in ROP treatment [44]. A trending topic in pediatric retina is the use of technology to capture and to transmit images from remote areas to specialty centers at big cities in developing countries like ours. In India, there is a very interesting program called the Karnataka Internet Assisted Diagnosis of Retinopathy of Prematurity (KIDROP), where digital images are obtained by trained technicians in rural hospitals for later grading and interpretation by a specialist after uploading images to a software platform. A diagnostic opinion and management suggestions are then sent to the referring center where the patient is located, in order to provide a better care [45].

Questions emerge with the appearance of these new platforms: Is it reliable? A sensitivity of around 80 to a

100 % and a specificity of more than 90 % have been reported [46]. Evidently, good technical training for the obtaining of images is compulsory [47].

Clinical significant ROP (CSROP) is a term created for the purposes of the PHOTO-ROP (The photographic screening for retinopathy of prematurity) study [48] to recognize the fact that bedside ophthalmoscopy and digital fundus imaging are complementary. This term was designed to serve as a telemedicine referral threshold definition indicating the need for onsite examination by an experienced ophthalmologist in the interest of minimizing the likelihood of missing early treatable disease. Besides from the Type 1 ETROP, it includes the following:

1. Zone I, any ROP without vascular dilation or tortuosity,
2. Zone II, stage 2, with up to one quadrant of vascular dilation and tortuosity,
3. Zone II, stage 3, with up to one quadrant of vascular dilation and tortuosity,
4. Any vascular dilation and tortuosity noted in eyes for which ridge characteristics were not interpretable (not imaged or poor image quality), and
5. Any ROP noted in eyes for which disk features (plus disease) were not interpretable (not imaged or poor image quality).

Using the CSROP criteria with indirect ophthalmoscopy, CSROP developed in 57.8 % of eyes with 22 % progressing further to ETROP type I prethreshold ROP; using digital images, CSROP developed in 72 % of the eyes, with 38 % progressing further to ETROP Type I prethreshold ROP [48].

Conclusions

A better understanding of the disease has been achieved as a result of the images obtained by FA and SD-OCT. FA is a very useful tool for management decisions and to differentiate ROP from other entities similar to it; the SD-OCT also helps understanding morphologic development of the macula in patients with ROP, and to acknowledge the vitreoretinal interface at different zones of the retina in the context of ROP. Anti-VEGF therapy has revolutionized the treatment of the disease as a monotherapy or as an adjunct therapy (laser, cryotherapy, and/or surgery). In case patients need surgery, the lens-sparing vitrectomy with a small caliber surgery via pars plicata should be the first choice. Retcam and telemedicine allow timely diagnosis in remote areas.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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