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Keywords

Retinopathy of prematurity (ROP) • Threshold ROP • Plus disease • Neovascularization • Avascular retina

Retinopathy of prematurity (ROP) is an iatrogenic disease. Prior to 1940 it did not exist in humans and until 1941 no ophthalmologist had ever seen such case. That changed in 1940 when Dr. Martin Couney unveiled the country's first incubators for premature children that had pure oxygen to supplement the incubation chamber at the World's Fair in New York City. The following year, Dr. Theodore Terry in Boston, documented the first case of bilateral retrolental fibroplasia [1]. In the ensuing 10 years, it was estimated that approximately 7,000 premature babies in the United States went blind. It was not until 1986 that an international cooperative group formed and established the CRYO-ROP trial. The goal of the trial was to determine the natural history of this new disease and whether ablation of the avascular retina with cryotherapy would reduce the risk of blindness. To allow the international investigators to share data, the study established the International Classification of Retinopathy of Prematurity (ICROP). This system described the status of the disease based on three parameters: zone, stage, and presence of plus disease [2]. Taken together, these three measures determined whether a patient had mild

ROP, pre-threshold ROP, or threshold ROP. This status would then determine the patient's schedule for follow-up as well as need for treatment.

Zone

Because the cardinal feature of ROP is the presence of avascular retina, the study created three zones that characterized where the normal retinal vasculature was present. The primary criterion for creating zones was that the physician would be able to make the determination based on indirect ophthalmoscopy alone (Fig. 2.1).

ZONE 1: Those children with the most posterior ROP where the normal retinal vessels had very little growth were termed Zone 1. Patients with Zone 1 had their retinal vessels extended from the optic nerve out to the periphery but not beyond the macula. To assist the examining ophthalmologist in determining whether a patient was in Zone 1, the study defined it as a circle centered at the optic nerve that had a radius twice the distance from the optic nerve to the fovea (Fig. 2.2a). To qualify as being in Zone 1, the examiner only needed to identify one clock hour where the retinal vessels stopped within the region. For a quick way to determine Zone 1, an examiner using a 28 diopter lens can place the edge of the lens to just encompass the optic nerve on one side of the image field. The other side of the lens would then be the edge of the Zone 1 (Fig. 2.2b). This technique is an easy way for the

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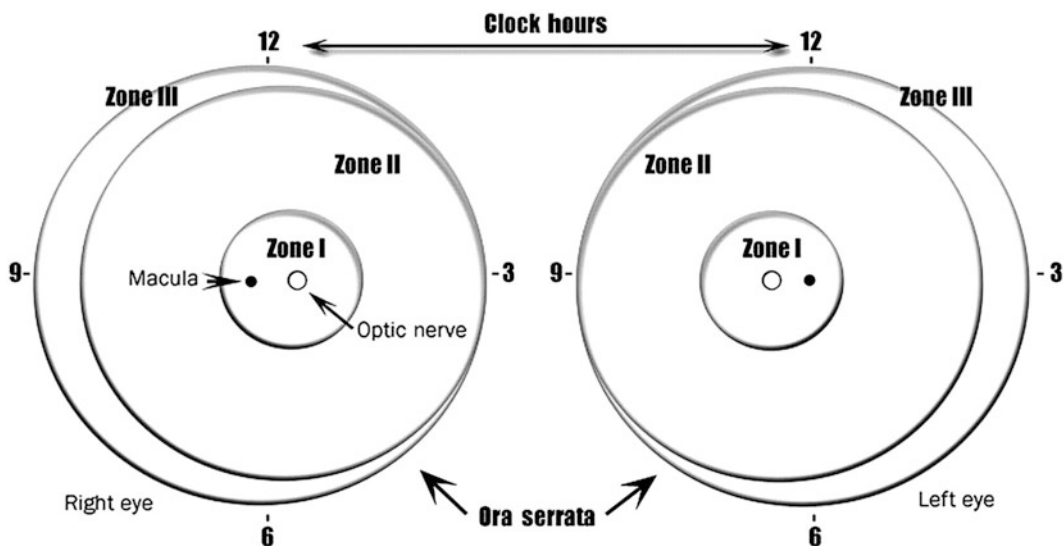


Fig. 2.1 ICROP exam form: standard form for documenting Zone and stage as well as presence of Plus disease

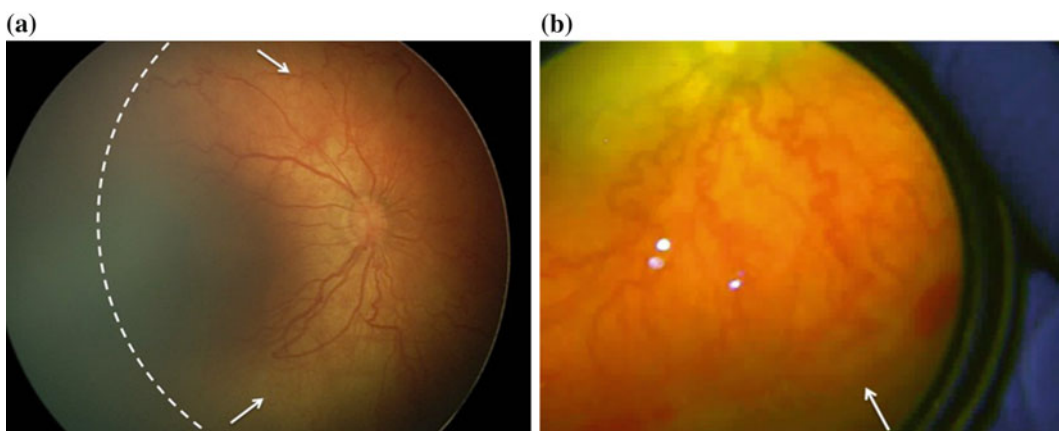


Fig. 2.2 **a** Example of Zone 1 ROP using a RetCam image. The *white dotted line* marks the edge of Zone 1. The *white arrows* show areas where the vascularized retina stops short of the Zone 1 border. **b** Example of Zone 1

ROP using a digital indirect ophthalmoscope and a 28 diopter lens where the optic nerve and the end of the vascularized retina (*white arrow*) can be seen in the same field of view

examiner to determine Zone 1 as long as the optic nerve is in view with a 28 diopter lens.

ZONE 2: This region is defined as retinal vessels that have extended past Zone 1 but remain within a larger circle that has a radius extending from the optic nerve to the nasal ora serrata (Fig. 2.3). From a practical standpoint, this would be an exam where the patient is not in Zone 1 but the retinal vessels do not extend all the way to the nasal ora serrata. Although the

retinal vascular development usually has equal growth from the optic nerve in all directions, there are times that it can be asymmetric with the vessels extending all the way to the nasal ora serrata but falling temporally into Zone 2 in which case the patient would still be classified as Zone 2.

ZONE 3: This region is defined as the remaining retina beyond Zone 2 and mostly represents the most peripheral temporal retina. This

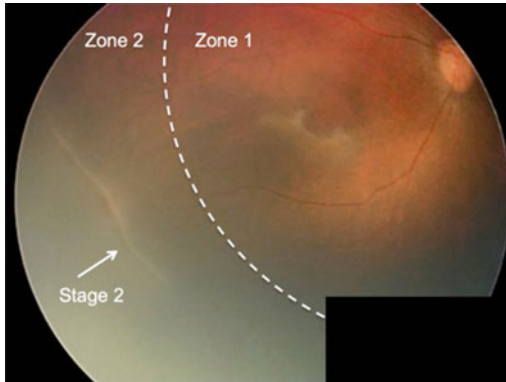


Fig. 2.3 Example of Zone 2 stage 2 ROP using a RetCam image. The vascularized retina extends beyond the border of Zone 1 (white arrow)

area can quickly identify when the retinal is fully vascularized nasally and the temporal aspect requires depression to visualize adequately.

Stage

Once the Zone has been identified, the next step is to determine the level of ROP at the interface between the vascular and avascular retina. Fundamentally the stage represents various levels of evolution of the pathologic angiogenesis. The neovascularization typically occurs at the edge of the vascularized retina. This neovascularization grows in a disorganized fashion that starts off as a white flat demarcation line. This is the very early phase of the process. As the pathologic neovascularization progresses, the vessels begin to accumulate at this location leading to an elevation/bump (some refer to the appearance of a “speed bump”). As the process continues the neovascularization begins to spill into the vitreous. This is the tipping point in the disease since the next phase is to recruit scar tissue along with the now vitreous involved vessels that can lead to a tractional detachment and blindness. To describe this, the CRYO-ROP study defined the different stages as follows:

Immature retina: when the retinal vessels stop and there is no visible demarcation line. This can be a challenge to identify because in the early exams there are often no clear landmarks to look

for. Some people informally refer to this as stage 0 although this is not a terminology used by ICROP.

Stage 1: The retinal vessels stop and then a linear flat white line is present that usually runs the circumference of the vascular retina.

Stage 2: The neovascularization is now accumulating and has developed thickness that manifests as a linear bump (speed bump). Importantly, the neovascularization remains along the surface of the retina and is not beginning to extend off the retina into the cortical vitreous (Fig. 2.3).

Stage 3: The neovascularization has now been accumulated at the edge of the vascularized retina so that it is now extending into the vitreous. ICROP has called this extra retinal fibrosis proliferation. In cases of Zone 2 and Zone 3, this will at times be described as a sausage shaped stage 3. Unlike the white/pink color of stage 1 and 2, stage 3 will often have a red appearance consistent with the increased blood being shunted through the accumulating stage 3 (Fig. 2.4a, b). In more posterior Zone 1 disease, the stage 3 can appear as a direct extension of the normal retinal vessels but extending tangentially over the avascular retina. This is in contrast to the typical stage 3, which has the sausage-shaped appearance. Some refer to this as flat neovascularization [3].

Stage 4: As the stage 3 progresses to grow into the vitreous it can form a continuous sheet coming up from the edge of the vascularized retina. The appearance of a sheet/membrane is an ominous finding and often is a precursor to a cicatricial phase that can induce vitreous organization around the vascular sheet. This scar tissue can grow toward the vitreous base/posterior lens capsule resulting in traction, distortion, and

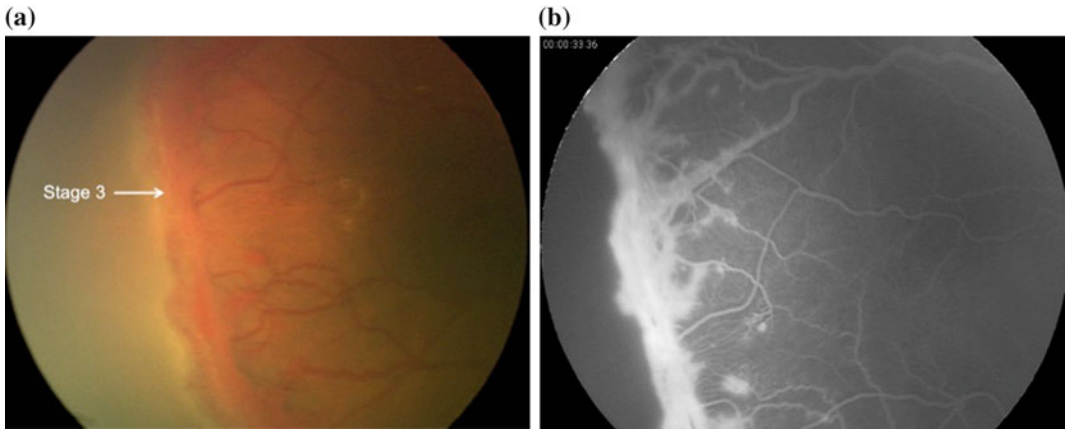
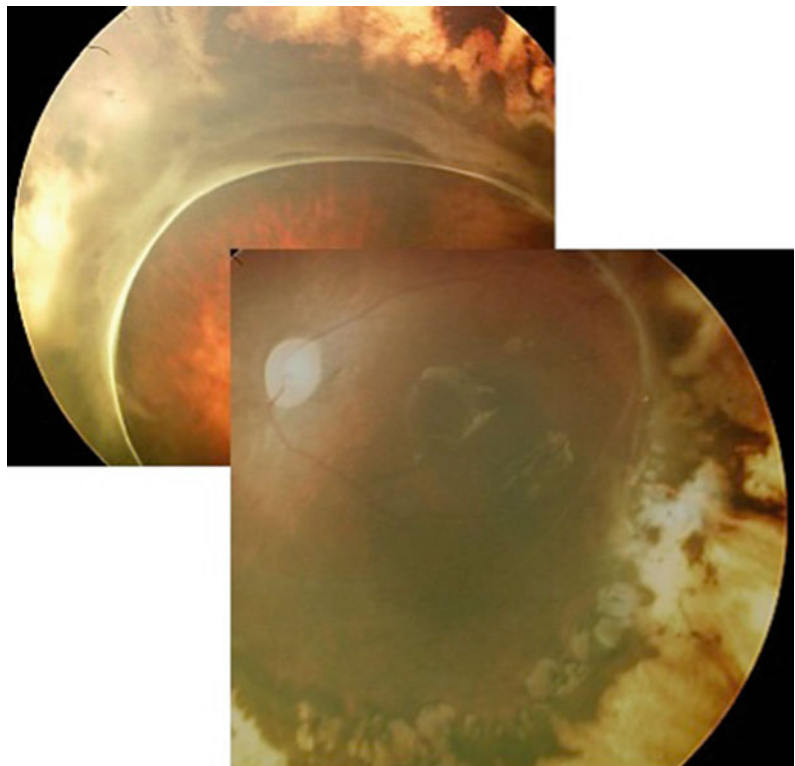


Fig. 2.4 **a** Stage 3 present temporally in the right eye (*white arrow*). **b** Fluorescein Angiography showing stage 3 at the edge of the vascularized retina

even detachment. Stage 4 occurs once the scar tissue causes enough traction to create a tractional detachment. Stage 4a describes a detachment that involves the peripheral retina that does not extend into the macula (Fig. 2.5). Stage 4b is when the traction extends more

posteriorly and involves the macula itself. The detachment usually starts in the temporal periphery although can also involve the nasal retina as well. While stage 1–3 occurs prior to treatment, stage 4 can occur after treatment and may be accelerated by the absence

Fig. 2.5 Stage 4A detachment with an annular ring of fibrosis present tugging on the retina leading a tractional detachment



of vascular endothelial growth factor posttreatment leading to an accelerated cicatricial phase.

Stage 5: When stage 4 progresses, it can lead to a total retinal detachment termed stage 5. This is funnel detachment with generally traction in all four quadrants. Stage 5a refers to an open funnel while stage 5b refers to a closed funnel.

Plus Disease

ROP is characterized by progressive changes in the retinal vasculature. As the pathologic neo-vascularization progresses, it creates collateralization resulting in increased in blood flow. Clinically this is manifested as vascular dilation and tortuosity. At the beginning, these vascular changes are more apparent in the peripheral vessels adjacent to the shunt and may even precede the clinical detection of stage 3. As the stage 3 progresses, the peripheral dilation and tortuosity is sometimes described as arborization or decreased branching angle of the vessels. These vascular changes in the periphery can ultimately progress more posteriorly resulting in Plus disease. The CRYO-ROP study characterizes Plus Disease as dilation and tortuosity of the vessels

exiting the optic nerve and involving at least six clock hours of the nerve (Fig. 2.6a). There was a standard photograph that was given as a reference (Fig. 2.6b). It is important to understand that the dilation and tortuosity of the peripheral vessels often seen with stage 3 do not constitute Plus Disease and that this term only refers to the nature of the vessels adjacent to the optic nerve.

The presence of Plus disease is now a key element in determining whether a patient qualifies for treatment. One fundamental problem with the definition is that it relies on the observer's own perception of what constitutes dilation and tortuosity. Studies have shown that even among experienced ROP examiners, there can be a wide variation on which exams qualify for Plus disease [4, 5]. There is also a modified term of Pre-plus disease, which is defined as vascular dilation and tortuosity that do not qualify as Plus disease [6].

Pre-threshold

One goal of the original CRYO-ROP Study was to identify eyes that would be at high risk of needing the treatment. These patients were identified as pre-threshold which included patients who were in Zone 1 (no Plus or stage 3)

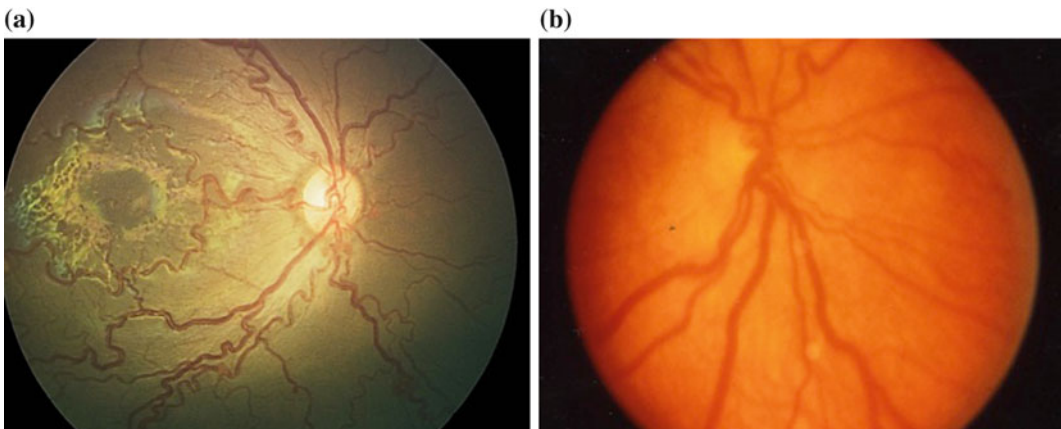


Fig. 2.6 **a** RetCam photography showing dilation and tortuosity of the posterior vessels as they exit the optic nerve. **b** Standard photograph showing Plus disease

or Zone 2 with Plus or stage 3 but not both. These children were placed on a more frequent examination schedule of at least every week or sooner as opposed to the recommended 2 week interval for patients with milder ROP.

Threshold

Threshold refers to an eye that has progressed beyond pre-threshold to include Zone 1 or Zone 2 with Plus disease and 5 continuous clock hours or 8 discontinuous clock hours of stage 3. In the CRYO-ROP study, patients with Threshold ROP received laser treatment or cryotherapy for avascular retina.

Early Treatment ROP Trial

Although patients with threshold ROP in Zone 2 did well, the Zone 1 patients still had a high failure rate and so a follow-up study, the Early Treatment for ROP (ETROP) trial [7–9], was started. This trial was designed to allow treatment earlier for those patients who were at a very high risk rather than waiting for full Threshold ROP. In this trial, pre-threshold was subdivided into Type 1 and Type 2. Type 2 was the milder form and included eyes in Zone 1 with no plus or stage 3 or eyes in Zone 2 with stage 3. Type 1 was any eye with Plus disease or a Zone 1 eye that developed stage 3. With this new criterion of Type 1 pre-threshold, the average time of laser treatment was now on average two weeks earlier and resulted in a reduction of the failure rate in Zone 1 disease.

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Retinopathy of Prematurity

Current Diagnosis and Management

Kychenthal B., A.; Dorta S., P. (Eds.)

2017, VIII, 155 p. 77 illus., 71 illus. in color., Hardcover

ISBN: 978-3-319-52188-6