Pediatric Vascular Retinopathies

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Abstract
Pediatric vascular retinopathies involve children from their birth through their whole lifespan. They include acquired retinopathies like retinopathy of prematurity (ROP), congenital lesions like Coats disease, and genetic vasculopathies as in familial exudative vitreoretinopathy, incontinentia pigmenti, or Norrie’s disease. The latter all share a common pathophysiological mechanism implicating the WNT signaling pathway. They are dominated by ROP and its devastating consequences if not properly addressed. Differential diagnosis can be challenging: medical history, family history are fundamental elements, and clinical characteristics need to be detailed with wide field angiography. The most effective treatment is laser ablative therapy of the ischemic retina or vascular anomalies in early stages of these diseases, vitrectomy surgery addressing the most severe ones with a poorer anatomical and functional prognosis. Anti-vascular endothelial growth factor is a helpful tool in these conditions, but should be used with caution in developing children.

In this article, we will focus on pediatric vascular retinopathies that can benefit from an effective treatment allowing resolution and conservation of the visual function. The classification of retinopathies is presented in Table 1.

Acquired Vascular Retinopathies: Retinopathy of Prematurity

Introduction
Retinopathy of prematurity (ROP) was first described in 1942 by Terry, with the survival of premature babies. It was only in the 1950s that the role of oxygen was identified, leading to the monitoring of oxygen therapy in premature infants. After a phase of increased mortality due to oxygen restriction in the 1960s, a careful monitoring of oxygen administration resulted in reduced mortality in the eighties, but persistent ROP; the use of artificial surfactant and maternal steroids have significantly diminished the rate of severe retinopathies. This trend is counter balanced by the survival of extremely premature infants and always lower birth weights.

It is responsible for over 50,000 cases of blindness worldwide and is the leading cause of treatable blindness in developed countries [1]. With increased survival of premature infants in developing countries, a new epidemic is taking place in these regions.

Pathophysiology
The normal development of retinal vessels is centrifugal and takes place from 16 weeks gestation up to the term. In premature infants, the vessel
development is not finished and immature subject to the influence of general and local factors [2]; it goes through 3 phases after birth:
1. Interruption of vascular development due to oxygen administration
2. Relative hypoxia due to metabolic demand (infection, general status)
3. Abnormal and abundant vascular development due to high levels of induced angiogenesis factors (IGF1, vascular endothelial growth factor, VEGF)

Classification
The classification of ROP has been revised in 2005 by the international committee for ROP and takes into account the vascular status, the geographical extent, and the evolutivity of the retinopathy [3].

Vascular Status
Stage 1: demarcation line
Stage 2: ridge (intraretinal neovascularization; Fig. 1)
Stage 3: thickened ridge and extraretinal neovascularization (Fig. 2)
Stage 4: partial retinal detachment
Stage 4A: macula preserved
Stage 4B: macula involved (Fig. 3)
Stage 5: total retinal detachment (open funnel or closed funnel; Fig. 4)

Geographical Extent
Zone 1: posterior retina, zone seen with a 28 or 30D lens centered on the disc (2 disc to fovea radius; Fig. 5).

Zone 2: circled zone centered by the disk up to the nasal ora serrata
Zone 3: up to the temporal ora serrata.

Evolutivity
It is defined as “plus” disease. This term characterizes dilation of retinal veins and arterial tortuosity as the disk margin in 2 quadrants or more: these clinical features are evaluated in comparison to a picture of the CRYO-ROP study defining plus disease [4].

A particular form of severe retinopathy has been defined as “aggressive posterior retinopathy” (APROP; Fig. 6): it develops in zone 1 with no thick ridge but a wide anastomotic neovascular meshwork, which is sometimes difficult to identify when optical media are not clear.

Treatment
The large CRYO-ROP randomized studies conducted in the 1980’s have shown the benefit of ablating the peripheral non vascularized retinal zones [4]. The “threshold” stage was defined as having a 50% risk of retinal detachment, and corresponds to stage 3 retinopathy with plus disease in 5 contiguous meridians (Table 2). Laser therapy has replaced cryo therapy and holds less side effects leading to earlier treatment of patients [5].

The “early treatment ROP” study published in 2003 [6] is now the reference for indication of laser treatment in ROP. It defined 2 types of ROP outlining the evolutivity of the retinopathy: type 1 had a 15% risk or higher of unfavorable outcome as opposed to type 2, having a lower than 15% risk (Table 3).

ETROP type 1: zone 1, any plus disease or stage 3; and zone 2, stage 2 or 3, with plus disease.
ETROP type 2: zone 1, any stage without plus disease; and zone 2, stage 2 or 3 without plus disease.

Laser Treatment
Laser ablation of the non vascularized peripheral retina is performed in type 1 ETROP eyes. Under general anesthesia, laser is applied nearly conflu-
Fig. 1. Stage 2 ROP zone 2.

Fig. 2. Stage 3 ROP, zone 1.

Fig. 3. Dry retinal fold, stage 4B ROP.

Fig. 4. Stage 5 ROP.

Fig. 5. 3 zones defining the extent of ROP.
Regression of the retinopathy takes place in the following days in 90% of the cases, allowing preservation of the posterior pole. Failure of the treatment is due to untreated ischemic retinal areas, or mostly to APROP cases.

Other complications of the treatment include induced Myopia (15% compared to 50% in the CRYO-ROP study), cataracts (0.5%) [5].

Anti-Vascular Endothelial Growth Factor VEGF is a major factor involved in retinal angiogenesis and high concentrations have been identified in severe retinopathy cases.

Mercado first used Anti-VEGF for the treatment of severe ROP without any adverse effects.

A randomized control study in 2011, showed the superiority of half adult dose of Bevacizumab in APROP and posterior severe retinopathy over conventional laser treatment, allowing regression of the ridge and almost normal peripheral vascular growth compared to the large scarring of the posterior retina after laser ablation [7].

Although no adverse report has been presented with the use of Anti-VEGF, the latter has to be used with caution in infants, because of the role of VEGF in normal central nervous system and lung development and maturation. Sato has shown that intravitreal injection of half-dose of bevacizumab leads to systemic drop in VEGF concentration for

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<th>Table 2. Results of the CRYO-ROP study</th>
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<td><strong>Anatomical failure, %</strong></td>
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<td>3 months</td>
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<td>Control</td>
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<td>Treated</td>
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<th>VA &lt;20/200, %</th>
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<tr>
<td>5 years</td>
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<td>Control</td>
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<td>Treated</td>
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<th>Table 3. Results of the ETROP study</th>
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<td><strong>Anatomical failure, at 6 years (type 1), %</strong></td>
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<td><strong>Functional failure at 6 years (&lt;1.85 c/day) (type 1), %</strong></td>
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<td>32.8</td>
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<td>8.9 (p &lt; 0.001)</td>
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Fig. 6. APROP.