Nasal versus temporal preretinal vasoproliferation in retinopathy of prematurity

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SUMMARY Nasal preretinal neovascularisations have been observed to develop at least two weeks earlier than those on the temporal side in more than a third of premature babies with retinopathy of prematurity (ROP) stage 3, weighing between 690 and 1030 g. All these babies were assigned for cryotherapy. This interesting observation is discussed in relation to retinal vascular development and the pathogenesis of ROP.

The embryonic retina remains avascular until the fourth month of fetal development.1-3 At 4 months spindle cells are found in Bergmeister's precapillary cone surrounding the walls of the hyaloid artery and its veins.1 From the walls of the venous channels on either side of the hyaloid artery the spindle cells undergo active mitosis and begin their migration into the nerve fibre layer at the 16th week of embryonal life.1 These undifferentiated spindle cells continue to advance towards the ora serrata, so that they always form the peripheral margin (vanguard) of the developing capillaries.4 The capillary bed with the vanguard of spindle cells appears to spread centrifugally, so that by the eighth fetal month the primitive capillary network extends almost to the ora serrata nasally but only to the equator temporally.1,3,4 It is therefore obvious that through all stages of retinal development the avascular area of the developing temporal retina is much larger than the avascular area of the nasal retina. Consequently we should expect that in stage 3 retinopathy of prematurity (ROP) the active neovascular proliferations would be much more extensive and appear earlier in the temporal retina than in the nasal retina.

We present here an interesting observation on the development of nasal versus temporal vasoproliferative disease in ROP stage 3, found in premature babies born between the 26th and 28th weeks of gestation and with a birth weight less than 1250 g.

Materials and methods

During the years 1985-7, 85 premature babies weighing under 1250 g, born at the age of 28 weeks or less, were examined in the Neonatal Intensive Care Unit (NICU). The first fundus examination was performed at the age of 3 to 4 weeks. When the avascular area was found to be located in Zone I or II, the subsequent examinations were performed at least once a week. When ROP stage 3 (moderate) was diagnosed, cryotherapy was performed according to a protocol described by Ben-Sira et al.6

Results

Seventeen out of 85 premature babies (20%) were found to have ROP stage 3 and subsequently underwent cryotherapy. In six of the 17 cryotreated babies (35%) with ROP stage 3 the vasoproliferative disease was found to begin at least two weeks earlier in the nasal side of the retina than the temporal side (Table 1). Five of the six babies weighed less than 1000 g and one weighed 1030 g. In five babies cryotherapy was performed first on the nasal retina and subsequently, owing to progression of the active vasoproliferative disease temporally, on the temporal side. In only one baby was the vasoproliferative disease confined to the nasal retina, while ROP stage 2 only was noted on the temporal side (Table 1). Cryotherapy was therefore applied to the nasal avascular retina and not to the temporal side. No difference was found in the...
Table 1  Timing and extent of nasal versus temporal ROP stage 3

<table>
<thead>
<tr>
<th>Case</th>
<th>Weight (g)</th>
<th>Gestational Age (weeks)</th>
<th>ROP timing (weeks after birth), stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nasal side</td>
</tr>
<tr>
<td>1</td>
<td>750</td>
<td>26</td>
<td>Both</td>
</tr>
<tr>
<td>2</td>
<td>1030</td>
<td>27</td>
<td>Both</td>
</tr>
<tr>
<td>3</td>
<td>990</td>
<td>28</td>
<td>Both</td>
</tr>
<tr>
<td>4</td>
<td>690</td>
<td>28</td>
<td>Both</td>
</tr>
<tr>
<td>5</td>
<td>910</td>
<td>26</td>
<td>Both</td>
</tr>
<tr>
<td>6</td>
<td>860</td>
<td>27</td>
<td>Both</td>
</tr>
</tbody>
</table>

*Stage 2 only.

clinical course of ROP stage 3 whether it started in the nasal retina or the temporal. Moreover, vasoproliferative disease in the nasal retina was found to regress after cryotherapy in the same manner as it did on the temporal side.

Discussion

Cogan' and Patz'' have shown that at 8 months of embryonic life the retina is completely vascularised only in the nasal periphery, whereas the temporal periphery is not completely vascularised until shortly after birth of the full-term infant. At the embryonal age of 8 months the developing capillaries have just reached the equator in the temporal retina (Fig. 1). Since the temporal periphery is the last part of the retina to become vascularised, the temporal retina has larger ischaemic areas than the nasal retina. This pattern of vascularisation probably explains the greater susceptibility of the temporal retina to ROP and may even explain the occasional case of ROP occurring in the full-term infant's temporal retina.

Extensive animal studies have shown that the retinal vessels are susceptible to oxygen damage only when the retina is incompletely vascularised. In addition the premature baby's retinal vasculature was found to be vulnerable to many other noxious factors which may be associated with ROP.

We would therefore expect that a premature baby born before the 28th week of gestation, and weighing less than 1250 g, would develop more extensive ischaemic vasoproliferative disease, and much earlier on the temporal than the nasal retina. It is an interesting fact that in more than a third of the cases reported here (35%) ROP stage 3 with confluent preretinal neovascularisation developed at least two weeks earlier in the nasal retina than the temporal. All these babies except one weighed less than 1000 g. Later on, following cryoablation of the nasal retina, the vasoproliferative disease progressed to the temporal side, and was subsequently treated by further cryoablation in all babies except one. In the last baby ROP of the temporal retina remained at stage 2, and there was therefore no indication for cryotherapy. In agreement with our findings, Fielder et al reported that the first visible changes of acute ROP can often be found in the nasal retina, particularly in the more immature baby.

Unfortunately we cannot find any firm explanation for this unexpected observation. It should be stressed that ROP is a multifactorial disease, whose pathogenesis is still incompletely understood. It may well be that peripheral retinal avascularity and subsequent ischaemia are not the only pathogenic factors. According to other hypotheses, such as the 'spindle cell theory' as well as that of tissue oxygen radicals, the temporal retina should have no priority as the 'place of less resistance.'

References

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Accepted for publication 15 April 1989.