Retinopathy of prematurity in infants of birth weight >2000 g after haemorrhagic shock at birth

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Abstract
Background—The risk of retinopathy of prematurity (ROP) is associated with low birth weight and low gestational age. For ROP screening examination is recommended in infants weighing \(<1500\) g or of less than 32 weeks’ gestational age.

Methods—From 1991 ROP screening was performed in 452 premature infants with either a birth weight \(<1500\) g (n=303) or a birth weight \(>1500\) g (n=149) and who required additional oxygen supplementation or underwent surgery with general anaesthesia before estimated term.

Results—Unexpectedly, three infants with birth weights between 2080 and 2325 g and a gestational age of 32 or 33 weeks developed stage 2 or 3 ROP. One of these underwent cryocoagulation. In three infants, preterm birth was induced by sudden placental abruption with severe prenatal blood loss followed by haemorrhagic shock. The umbilical cord packed cell volume was reduced to 0.14–0.19 (normal 0.43–0.63). All three infants underwent surgery with general anaesthesia within the first weeks of life. Of the remaining 449 infants none with a birth weight \(>1650\) g developed any stage of ROP.

Conclusion—Severe prenatal blood loss requiring blood transfusions and surgery with general anaesthesia may induce higher stages of ROP even in infants with birth weights exceeding the usual screening criteria.

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In the last decade several studies have determined the natural course of retinopathy of prematurity (ROP). \(^{1-12}\) Risk factors for the development of higher stages of ROP have been established \(^9\) \(^{11}\) \(^{12}\) and the benefit of either cryotherapy \(^8\) \(^{13}\) or laser treatment \(^{14}\) \(^{15}\) in eyes with ‘threshold ROP’ (according to the Cryo-ROP study criteria) \(^7\) has been shown. The early detection of stage 3 ROP is crucial for the exact timing of the treatment. \(^{17}\) When treatment is delayed, development of retinal detachment and subsequent very low visual acuity or blindness is more likely. \(^{18}\)

To date, ophthalmoscopic screening examinations are a routine procedure in neonatal care units. \(^{19}\) \(^{20}\) The purpose of ROP screening is the early detection of children with threshold disease. In several countries guidelines for screening programmes for the early detection of ROP have been recommended. \(^{12}\) \(^{19-22}\) Because birth weight and gestational age are the most important risk factors for the development of ROP, \(^5\) \(^{10}\) \(^{12}\) inclusion criteria are generally based on these easily obtainable data. The maximum birth weight up to which infants should be examined varies from 1251 g in the USA \(^9\) to 1500 g in European countries. \(^{10}\) \(^{22}\) Most authors agree that it is sufficient to examine all infants with a birth weight below 1500 g or a gestational age <32 weeks.

In this study we report the clinical findings in three infants with a birth weight >2000 g and a gestational age of 32 and 33 weeks, who unexpectedly developed stage 2 or 3 ROP. These children survived severe maternal and fetal bleeding and were severely ill during the first months of life. Surgery with general anaesthesia was necessary in all three infants.

Materials and methods
The ophthalmic and paediatric charts of three infants who unexpectedly developed stage 2 or 3 ROP were evaluated retrospectively. Regarding the ocular findings, the data were compared with a consecutive series of 449 premature infants who were examined between March 1990 and February 1995 in the ophthalmic department. During that time our ROP screening criteria included all infants with a birth weight <1500 g (n=303) and infants with birth weight >1500 g who required additional oxygen supplementation (n=123) or underwent surgery with general anaesthesia before estimated term (n=23). The first examination was performed 5–6 weeks after birth. \(^9\) Dilatation of the pupils was performed by a combination of tropicamide 0.5% and phenylephrine 2.5%. After topical anaesthesia a lid speculum and scleral depressor were used to visualise the ora serrata or the anterior border of the retinal changes. Examinations were done with an indirect ophthalmoscope. The assessment of stages, grading of ROP, and documentation of the fundus changes were based on the international classifications. \(^{23}\) \(^{24}\) Threshold retinopathy was diagnosed and treated according to the criteria of the Multicenter Trial of Cryotherapy for ROP. \(^1\)

Regarding the paediatric findings, the data were compared with a consecutive series of 717 preterm infants admitted to the paediatric department in the same period.

Results

PAEDIATRIC FINDINGS
The clinical data at birth of all three cases are summarised in Table 1. In all three cases severe
intrauterine bleeding with fetal blood loss induced the preterm birth. These infants had severe peripartial asphyxia, acidosis, and a low or non-measurable blood pressure. The umbilical cord packed cell volume (PCV) values were very low (0.14–0.19) and immediate blood transfusions were required. In 717 other infants admitted to the paediatric department the lowest PCV was 0.27 and the mean PCV was 0.48 (normal range 0.43–0.63).

In all three cases additional diseases developed during the first weeks of life. In case 1 the infant received mass transfusion within the first hours of life. An amnion infection syndrome was suspected. A jejunal atresia was diagnosed and surgery in general anaesthesia was performed on day 2.

In case 2 mass transfusion was also necessary immediately after birth; this was followed by acute renal failure, respiratory distress syndrome, and later a chronic renal insufficiency. A duodenojejunial atresia was operated on with general anaesthesia on day 17. Additional surgery was necessary on day 43. A cholestatic icterus and a gastro-oesophageal reflux were present for 2 months. Severe cerebral defects remained during follow up.

In case 3 mass transfusion was also performed immediately after birth. A multiple organ failure developed after birth. A respiratory distress syndrome was present and additionally acute lung bleeding occurred on day 4. Chronic renal insufficiency induced systemic hypertension and subsequently cardiac failure. A transperitoneal dialysis with surgery in general anaesthesia on days 25 and 45 was performed. A coagulopathy and anemia developed later on.

**Table 1 Clinical data at birth**

<table>
<thead>
<tr>
<th>Case</th>
<th>Birth weight (g)</th>
<th>Gestational age (weeks)</th>
<th>Packed cell volume (%), PCV</th>
<th>PHHb</th>
<th>Mean blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2080</td>
<td>33 (+4)</td>
<td>0.18</td>
<td>6.93</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>2185</td>
<td>32 (+2)</td>
<td>0.14</td>
<td>7.02</td>
<td>Not measurable</td>
</tr>
<tr>
<td>3</td>
<td>2325</td>
<td>33 (+1)</td>
<td>0.19</td>
<td>7.03</td>
<td>30</td>
</tr>
<tr>
<td>Norm</td>
<td></td>
<td></td>
<td>0.43–0.63</td>
<td>7.26</td>
<td>35–55</td>
</tr>
</tbody>
</table>

UC=umbilical cord, UA=umbilical artery

weights ≥1300 g developed any stage of ROP. Six of the remaining 19 infants progressed to stage 3 ROP (birth weights 550–1010 g), and three of them underwent cryocoagulation or laser treatment.

**Discussion**

In the three infants described the preterm birth was induced by placental abruption with massive vaginal haemorrhage. Placental abruption often causes fetal anoxia and death. Surviving infants can be severely anaemic. In our patients the umbilical cord PCV values were very low (0.14–0.19) compared with the normal mean PCV of 0.48. The blood pressure was reduced below the normal range and a severe acidosis was present.

The retinal changes in the three infants would not have been detected if the recommended guidelines for ROP screening had been followed. Several hypotheses may explain the unexpected development of ROP in these children. For several years hypoxia and subsequent hyperoxia were suspected to be important for the pathogenesis of ROP, an overview of the various theories can be found at Palmer et al.23 Marked alterations in the retinal oxygen supply and subsequent damage to the retinal vasculature may have occurred at different times—directly after birth, during the first days of life, or within the following weeks.

One would expect that immediately after birth the loss of red blood cells, as indicated by the low PCV, and the breakdown of the haemodynamic regulation, as indicated by the low blood pressure, would have induced a severe hypoxia which may have damaged the retinal vasculature. Additional damage may have been caused by the severe acidosis.

Following the initial hypoxia due to the severe blood loss the multiple blood transfusions may have induced hyperoxia, especially because of the use of adult blood. Adult haemoglobin (HbA) has a lower affinity to oxygen compared with fetal haemoglobin (HbF). Therefore, the transfused blood releases more oxygen to the tissues. Moreover, the systemic iron overload caused by these transfusions may affect the defence systems against free radicals, which may have caused additional tissue damage.

In the first weeks of life the severe illness and the surgery with general anaesthesia may have induced multiple alterations in oxygenation, circulation, and other factors. These alterations may be additional factors in the development of ROP. However, in our population surgery with general anaesthesia in itself appears not to be associated with a higher risk of ROP; no other infant with birth weight above 1500 g who underwent surgery developed any stage of ROP.

We cannot determine whether blood loss, transfusions, abdominal surgery, or a combination of all factors induced the development of ROP in these infants. Placental abruption with severe fetal blood loss followed by transfusions of adult blood has been described previously as a risk factor for ROP development. It has not

**OPHTHALMOSCOPIC FINDINGS**

The three children were examined by ophthalmoscopy because they underwent surgery before estimated term. At the first examination 6 weeks after birth a zone 2 vascularisation was present in cases 1 and 2 and vessels reached into zone 3 in case 3. In case 1 the maximum stage of ROP was stage 2 in all 12 hours on both eyes. Spontaneous regression and complete vascularisation developed later. In case 2 cryocoagulation was performed on both eyes when stage 3+ had developed in 10 hours. Following treatment, complete regression of retinal changes occurred. In case 3 ROP progressed to stage 3 in 2 hours before spontaneous regression occurred.

Besides these three infants with a birth weight >2000 g no other infant with a birth weight >1650 g developed any stage of ROP. Of 43 infants undergoing surgery with general anaesthesia, none of 24 infants with birth weight
been demonstrated that this may occur in infants with birth weights \( > 2000 \) g. It can be argued, that none of the factors discussed above had any influence on development of ROP in these infants, because ROP has been observed even in some infants born at term with normal birth weight and without oxygen therapy.\(^{33,44}\) These findings, however, have to be questioned. In earlier reports, the final stage of retrolental fibroplasia has been described, but the course of progression of ROP has not been observed.\(^{32,33}\) In a few cases, a peripheral proliferative retinopathy has been observed.\(^{35}\) Other diseases may present with peripheral avascular retina, proliferative retinopathy, and retinal detachment.\(^{36}\) Autosomal dominant exudative vitreoretinopathy was first described as a separate entity in 1969\(^{37}\) and the gene locus was linked to chromosome 11.\(^{38}\) The linked exudative vitreoretinopathy has been reported only recently.\(^{40}\) Early retinal detachment is a sign of Norrie disease and may develop even in female carriers.\(^{41,42}\) Molecular genetic analysis revealed that Norrie disease, X linked exudative vitreoretinopathy, and X linked retinal dysplasia are allelic diseases with mutations in the Norrie disease gene.\(^{43,44}\) With our present understanding of pathogenesis and risk factors for ROP\(^{45}\) it seems very unlikely that ROP would develop in full term infants. In all such infants, a detailed evaluation of the family as well as a molecular genetic analysis must be required, before ROP may be diagnosed. In the infants described in this study family history was unremarkable. The combination of preterm birth and several risk factors for ROP suggest that ROP is the correct diagnosis in these three infants. The above mentioned diseases can be excluded, especially because spontaneous regression and subsequent normal vascularisation of the peripheral retina is not common in exudative vitreoretinopathy.\(^{47}\)

In conclusion, the findings in our infants demonstrate that those with severe illness may develop threshold ROP even when they weigh \( > 2000 \) g at birth and so would be excluded from ROP screening. We propose that premature infants with severe fetal blood loss (for example, umbilical cord PCV lower than 0.30) or other severe illness and with a birth weight \( > 1500 \) g should be examined.


