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Natural course of retinal development in preterm infants without threshold retinopathy

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Abstract In a consecutive series, 209 preterm infants with birth weights below 1501 g or a gestational age of ≤32 weeks were observed. Stage 3 retinopathy of prematurity (ROP) developed in 48 infants (23%) of between 32 and 46 weeks postconceptional age (PCA; mean, 37 weeks). Stage 3 ROP was not seen before 6 weeks after birth. Threshold ROP was seen and treated at between 34 and 42 weeks PCA (mean, 38 weeks PCA; $n=22$, 10.5%). A subgroup of 126 untreated infants were followed until complete retinal vascularisation. At estimated term, 38.7% of eyes with vessels ending in zone 3 at the first examination showed complete vascularisation as compared with 17.6% of eyes with vessels ending in peripheral zone 2 and none of those with vessels ending in central zone 2. Occurrence of ROP delayed retinal development. At estimated term, no eye with any stage of ROP showed complete vascularisation as compared with 35.4% of eyes without ROP. Regression of stage 3 ROP below threshold started in all cases before 56 weeks PCA.

Key words Retinopathy of prematurity · Preterm infants · Natural course · Cryocoagulation

Zusammenfassung In einer konsekutiven Serie wurden 209 Frühgeborene mit einem Geburtsgewicht unter 1501 g oder eine Schwangerschaftsdauer ≤32 Wochen beobachtet. Ein RPM-Stadium 3 trat bei 48 Kindern (23%) zwischen 32 und 46 postkonzeptionellen Wochen (PKW) auf, (Mittelwert: 37 PKW). Vor der 6. Lebenswoche wurde kein Stadium 3 gesehen. Ein behandlungsbedürftiges Stadium 3 trat zwischen 34 und 42 PKW auf (Mittelwert: 38 PKW; $n=22$, 10,5%). Eine Untergruppe von 126 unbehandelten Kindern wurde bis zur kompletten Netzhautvaskularisierung beobachtet. Zum errechneten Geburtstermin zeigten 38,7% der Augen mit Gefäßen in der Zone 3 zum Zeitpunkt der Erstuntersuchung eine komplette Netzhautvaskularisierung im Vergleich zu 17,6% der Augen mit Gefäßen in der zentralen Zone 2. Trat eine Frühgeborenenretinopathie ein, verzögerte sich die Netzhautentwicklung. Zum errechneten Geburtstermin hatte kein Auge mit einer Frühgeborenenretinopathie eine komplette Netzhautvaskularisierung – verglichen mit 35,4% der Augen ohne Retinopathie. Eine Regression eines Stadiums 3 ohne Therapie wurde nicht später als mit 56 PKW beobachtet.

Schlüsselwörter Frühgeborenenretinopathie · Frühgeborene · natürliche Entwicklung · Kryokoagulation

Introduction

The sequelae of retinopathy of prematurity (ROP) have been known since its first description by Terry [22]. Improvement of neonatal intensive care units increased the rate of survival of premature infants with birth weights below 1000 g from less than 10% in the 1950s to 30% for children weighing between 500 and 599 g and 91% for infants weighing between 1200 and 1250 g in 1987 [17]. The increased survival of extremely small premature infants with less vascularised retinas has produced a new population of infants with a high risk of developing ROP. The exact cause of ROP has not been determined [8, 11, 16]. It depends on the very low birth weight and low gestational age. The incidence of any stage of ROP is high (90%) in infants born weighing less than 750 g as compared with infants weighing 1000–1250 g (46.9%) [15]. The findings vary by gestational age in a similar manner. Infants born at up to 27 gestational weeks have been found to have some stage of ROP in 83.4% of cases as compared with 29.5% of the group with a gestational age of 32 weeks or more [15].

An international classification of ROP grading was established in 1984 [2]. The retina was divided into three zones and the extent of disease was described by the meridians (hours of the clock) involved. The retinal changes were divided into four stages. In 1987 the classification was modified [10]. Stage 4 was extended and a fifth stage of retinal detachment was added. The Cryo-ROP Study Group [3] defined recommendations for treatment; 5 or more continuous or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2 with plus disease (tortuosity and dilatation of vessels at the posterior pole) were called threshold ROP. It was reached in only 6% of all 4099 infants included in the Cryo-ROP study [3, 4]. The incidence was 15.5% for children with birth weights lower than 750 g and 2% for infants weighing between 1000 and 1250 g [15].

Most studies have described the development of the retina until threshold retinopathy, the incidence of and risk factors for ROP, the modalities of treatment and complications [1, 3, 12, 13, 18, 19]. The purpose of the present study was to define the time course of retinal vascularisation up to the development of threshold ROP and to examine the long-term natural course until complete retinal vascularisation in eyes below threshold retinopathy.

Patients and methods

Patients

In a consecutive series, patients were enrolled between March 1, 1991, and September 1, 1993. The criteria for examination included all infants with birth weights of less than 1501 g or a gestational age of 32 weeks or less. During the 2.5-year study period, 209 infants were seen. The mean birth weight was 1205 ± 366 g and the mean gestational age was approximately 28.7 ± 2.3 weeks. Multiple birth occurred in 25% of cases (52 children); (35 sets of twins, 13 sets of triplets and 4 sets of quadruplets). In five twin pairs we examined only one twin and in one triplet, only one infant.

To determine the natural course of retinal development, a subgroup was formed that included preterm infants with follow-up to complete retinal vascularisation. We excluded all children given treatment during the observation period. The subgroup comprised 126 premature infants with birth weights ranging between 500 and 2250 g who were born at 24–32 gestational weeks. Of the infants, 50% weighed 1250 g or less. More than half of all children were born at 28 gestational weeks or less. The mean birth weight was 1230 ± 337 g and the mean gestational age was 28.9 ± 2.0 weeks. Multiple birth occurred in 24.6% of cases (24 sets of twin and 7 sets of triplets).

Examination technique

The first examination was performed at 5–6 weeks after birth as based on the results of previous studies [1, 3, 4, 15]. Very immature children were examined in the incubator. Dilatation of the pupils was performed by a combination of tropicamide 0.5% and phenylephrine 2.5%, with one drop being applied to each eye three times at 10-min intervals. After topical anesthesia a lid speculum and a scleral depressor were used to visualise the ora serrata or the anterior border of the retinal changes. Examinations were done with an indirect ophthalmoscope and a hand-held lens. The assessment of stages, grading of ROP and documentation of the fundus changes was based on the international classifications [2, 10]. When complete vascularisation was present at the first examination, no follow-up examination was performed. If any avascular area or some stage of ROP was present, follow-up was determined according to the immaturity of the infant and the severity of retinal changes at between 1–4 weeks until the vessels extended to the ora serrata. According to the Cryo-ROP study criteria [3], we treated the avascular areas with either laser or cryocoagulation.

Results

In our study we included only 1 eye of each of the 209 children. Most children showed no difference in staging of ROP between the examined eye and the contralateral eye. An asymmetry of one stage of ROP was seen in 8 cases (3.8%). In these cases the eye with the more advanced retinal changes was included. In no case was a difference found between the two eyes concerning the zone of retinal vascularisation at the first examination.

Early course of retinal development

Stage 3 ROP was recognized in nearly a quarter of all preterm babies (48/209). The mean postconceptional age (PCA, gestational age plus postnatal age) at onset of stage 3 was 37 weeks (Fig. 1). Children of a lower gestational age needed more weeks after birth until onset of

stage 3 as compared with infants of higher gestational age. For example, children born at 24 weeks gestational age developed stage 3 ROP at between 10 and 15 weeks after birth as compared with infants born at 31 weeks gestational age, in whom stage 3 ROP appeared 6–10 weeks after birth.

The onset of stage 3 appeared as early as at 32 weeks PCA. Stage 3 was not seen before 6 weeks after birth. The latest occurrence of stage 3 ROP was observed in two children as late as at 45 and 46 weeks PCA, respectively; these two babies had undergone surgery for herniation 2–4 weeks previously. In all, 26/48 (54%) eyes with stage 3 ROP never reached the treatment threshold.

The mean age for threshold ROP was 38 weeks PCA (Fig. 2). The earliest observation of threshold ROP was recorded at 34 weeks PCA. All eyes reaching threshold ROP did so by 42 weeks PCA. Altogether, 22/209 (10.5%) infants underwent cryo- or laser coagulation.

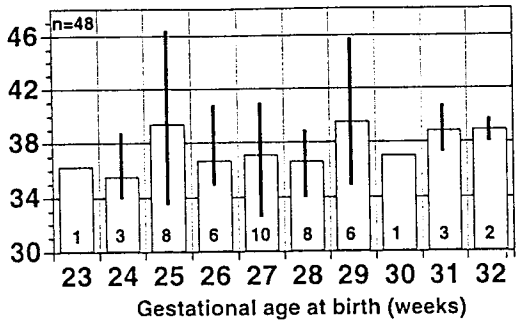

Fig. 1 Postconceptional age at onset of stage 3 in relation to the gestational age at birth. *Columns* indicate the mean onset for each gestational age at birth; *vertical bars* indicate the upper and lower ranges. *Numbers within the columns* indicate the number of infants for each gestational age at birth

Long-term follow-up

The natural course of retinal vascular development was observed to complete vascularisation in 126 untreated infants. In 5 preterm babies with stage 2 and stage 3 ROP the vascularisation did not extend to the temporal ora during a follow-up period of 9 months. In these eyes, vascularisation was considered to be final when retinal vascularisation remained unchanged over the following 3 months.

At the time of the first examination, 20 (15.9%) eyes showed a completely vascularised retina; 65 eyes (51.6%) with avascular peripheral retina never showed any evidence of ROP. In all, 41 (32.5%) eyes developed some stage of ROP. In 8% of cases (10 eyes), stage 1 was the highest active stage of ROP, and in 8.7% (11 eyes), stage 2 was the highest stage. Stage 3 below threshold ROP was reached in 15.9% of cases (20 eyes). At the first examination, 106 preterm babies had a peripheral avascular retina. In all, 57 eyes (53.8%) had retinal vascularisation confined to zone 2. In 21.7% of cases (23 eyes) incomplete vascularisation occurred at the beginning of zone 2, and in 32.1% (34 eyes) the vessels extended to peripheral zone 2. In 46.2% of cases (49 eyes) the vascularisation ended in zone 3.

Figure 3 shows the duration of retinal vascularisation depending on the zone at the time of first examination. All eyes ($n=20$) with complete vascularisation at this time were excluded. The duration of vascular development was longer in eyes with vessels ending in zone 2 as compared with zone 3. At estimated term, 38.7% ($n=19$) of eyes with vessels ending in zone 3 were completely vascularised. At the same time, 17.6% ($n=6$) of eyes with peripheral zone 2 vascularisation and none of the eyes with vessels reaching the beginning of zone 2 had complete vascularisation. After 45 weeks PCA there was al-

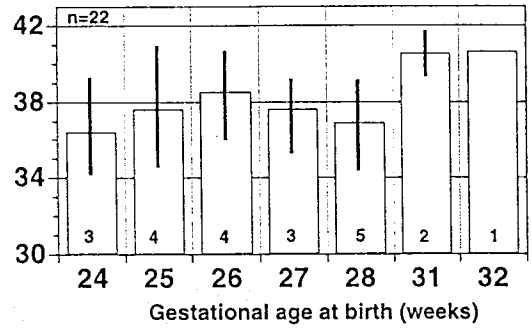

Fig. 2 Postconceptional age at the time of cryo- or laser coagulation in relation to the gestational age at birth. *Columns* indicate the mean age for each gestational age at birth; *vertical bars* indicate the upper and lower ranges. *Numbers within the columns* indicate the number of infants for each gestational age at birth

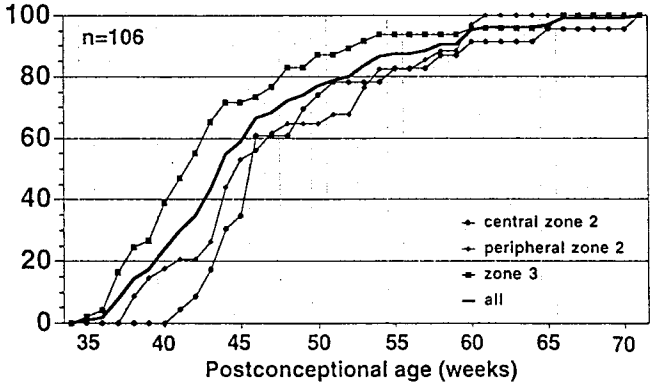

Fig. 3 Time course of retinal vascularisation in relation to different zones of vascularisation at the first examination. The *thick line* indicates the time course for all eyes. The time courses for eyes with zone 3 (*squares*, $n=49$), peripheral zone 2 (*rhombi*, $n=34$) and central zone 2 (*dots*, $n=23$) are indicated separately

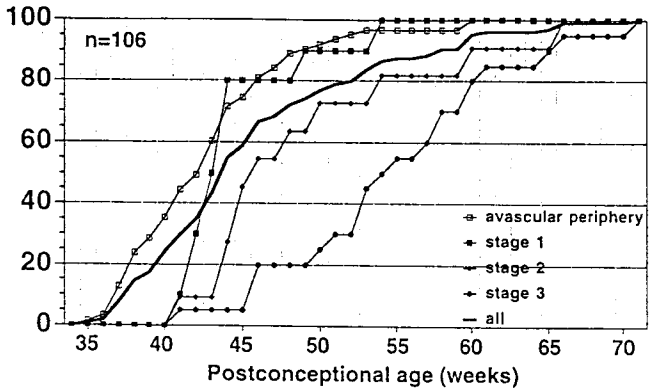

Fig. 4 Time course of retinal vascularisation in relation to different maximal ROP stages. The *thick line* indicates the time course for all eyes. The time courses for eyes with avascular periphery (*open squares*, $n=65$), stage 1 ROP (*filled squares*, $n=10$), stage 2 ROP (*rhombi*, $n=11$) and stage 3 ROP (*dots*, $n=20$) are indicated separately

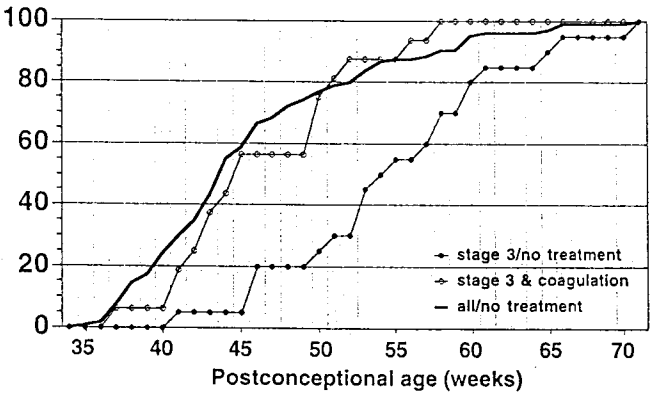

Fig. 5 Time course of retinal vascularisation in eyes with stage 3 ROP below threshold and eyes with treated threshold ROP. The time courses for eyes with stage 3 ROP below threshold (*dots*, $n=20$) and successfully treated threshold ROP (*open circles*, $n=16$) are indicated. For comparison, the time course for all untreated eyes is shown (*thick line*, $n=105$)

most no difference between peripheral and central zone 2. During the following observation period the time difference between zone 2 and zone 3 vascularisation was about 6 weeks.

The course of retinal development depending on the stage of ROP showed a delay for all stages (Fig. 4) as compared with avascular retina alone. By the time the children reached full term, no immature infant with any stage of ROP showed complete vascularisation as compared with 35.4% ($n=23$) of eyes with only avascular areas. One-half of the eyes with avascular areas or stage 1 ROP were vascularised at 43 weeks PCA. In all, 50% of the eyes with stage 2 ROP had completed vascularisation at 46 weeks PCA and those with stage 3 ROP, at 54 weeks PCA (3 months later than those with stage 1 ROP). Regression of stage 3 ROP was variable and sometimes difficult to define. Some eyes showed unchanged ophthalmoscopic findings at two or more follow-up examinations. At 56 weeks PCA, all children showed regression of the retinal findings.

All eyes with avascular retinas showed complete vascularisation at 60 weeks PCA. Eyes with stage 1 ROP had complete vascularisation at 54 weeks PCA. Eyes with stage 2 ROP did so at 66 weeks PCA and those with stage 3 ROP, at 71 weeks PCA.

Most children showed an equal time course of retinal development in both eyes. In two preterm infants one eye showed complete vascularisation 3 weeks later than the other eye.

In a comparison between eyes with stage 3 ROP below threshold ($n=20$) and eyes that reached the threshold, successfully underwent coagulation and had a complete follow-up ($n=16$) there was a difference in the time course of retinal vascularisation (Fig. 5). In eyes undergoing coagulation, complete regression of ROP and vascularisation of untreated retina was achieved in 50% of cases at 45 weeks PCA. At this time only 5% of the eyes with stage 3 ROP below threshold were completely vascularized. All eyes that received coagulation treatment showed complete regression of ROP at 58 weeks PCA. In all eyes that did not reach the treatment threshold, complete vascularisation was seen at 71 weeks PCA. In eyes with stage 3 ROP below threshold the time course of complete development was delayed for up to 8 months after full term.

Discussion

Several studies have reported the incidence of different stages of ROP [1, 3, 6, 9, 15, 18, 19]. Data on the time course of retinal development, however, are available from only a few studies [6, 9, 15]. The early course of retinal development shows a certain time span during which preterm infants are at risk for advanced stages of ROP. In our series, the onset of stage 3 ROP never occurred before 32 weeks PCA. Holmström et al. [9] observed in a series of 260 babies of ≤ 1500 g birth weight the onset of stage 3 ROP no sooner than 32 weeks PCA. In a series of 572 preterm infants of ≤ 1700 g birth weight [6], stage 3 ROP was not seen before 32 weeks PCA. The latest occurrence of stage 3 ROP in our series was seen at 46 weeks PCA (cf. Holmström et al. [9], 44 weeks PCA, and Fielder et al. [6], 47 weeks PCA). In most cases, stage 3 ROP developed previous to full term at a mean of 37 weeks PCA; this finding has been identical in all studies.

The time span of the risk for threshold ROP was even smaller and was seen at between 34 and 42 weeks PCA. Similar findings have been reported by Palmer et al. [15],

who evaluated 4099 infants of <1251 g birth weight enrolled in the Multicenter Trial of Cryotherapy of ROP. Only 5% of children developed threshold ROP before 33.6 weeks PCA. Another 5% developed threshold ROP later than 42 weeks PCA. The latest occurrence of threshold ROP was 48 weeks PCA. In general, the highest risk for stage 3 ROP appeared during the last few weeks before estimated term. Follow-up should be scheduled more often during that period. At infants of that age we perform examinations at 2-week intervals in eyes with large avascular areas without ROP and weekly in eyes with ROP. Comparable suggestions have been made by Palmer et al. [15]. After 42 weeks PCA the control schedule can be handled less tightly.

The time course of development of ROP seems to depend on the gestational age at birth. In our series no child had stage 3 ROP before the 6th week of life. This observation is in agreement with the findings of other autors [1, 3, 4, 9, 15]. Only very few babies with "rush" type ROP have been observed with threshold ROP before 6 weeks after birth [13]. Interestingly, children of a very low gestational age (24–25 weeks) needed a longer time tc develop stage 3 ROP as compared with children of 26 weeks gestational age or more. This has previously been noted elsewhere [6, 9, 18]. In accordance with our data and the findings in large studies performed in the United States [15, 18], Great Britain [6] and Sweden [9], it seems reasonable that preterm infants should be first examined at 31 weeks PCA and not prior to 6 weeks after birth. Follow-up can be stopped in eyes with less than stage 3 ROP at 2.5 months after estimated term. Reports on the long-term natural course of ROP are rare [6, 7]. In our series, in eyes with stage 3 ROP below threshold that showed spontaneous regression during follow-up, retinal vascularisation could be markedly delayed. In some eyes (4%), peripheral avascular areas could be seen at up to 1 year after birth; such areas represent the mildest sign of regressed ROP [10]. In these eyes the avascular areas did not change during the last 3 months and will probably remain avascular forever. In all the other children, the natural course of retinal development depended on the stage of ROP and on the zone of vascularisation at the first examination. As expected, eyes with zone 2 ROP at the first examination needed a longer time for complete vascularisation as compared with eyes with zone 3 ROP; however, a considerable variation was seen and the time difference between zone 2 and zone 3 vascularisation was about 6 weeks.

In our series, 35.4% of eyes with avascular retinas showed complete vascularisation at estimated term. Palmer et al. [15] stated that at estimated term, 80% of children with avascular retina had vessels that ended in zone 3. However, they did not specify when retinal vascularisation extended to the temporal ora serrata. In our series, any stage of ROP markedly delayed retinal development. At full term, no eye with ROP showed complete retinal vascularisation. Eyes with stage 3 ROP below threshold showed a mean retardation of retinal development of about 3 months. During the follow-up period, retinal changes are often very slow and it is sometimes difficult to decide whether regression has occurred. However, regression was seen in all cases at 4 months after full term, which is 5 weeks later than the observation made by Fielder et al. [6]. It seems reasonable that follow-up can be stopped in eyes with stage 3 ROP that show regression on two consecutive follow-up examinations. Only in children who undergo surgery or have other complications at that age is further control necessary. We observed one child who required laser treatment for threshold ROP after surgery for herniation during regressive stage 3 ROP. Flynn [7] have described that at 25–26 weeks after birth the process of ROP is ophthalmoscopically complete. This would be about 54 weeks PCA. At that time, 87.5% of infants in our series showed complete vascularisation.

The Cryo-ROP study showed after 1 year a significant difference between the control group and the treatment group [4]. In all, 47.4% of control eyes had an unfavorable outcome as compared with 25.7% of eyes that had received cryotherapy. Therefore, some investigators have suggested that a lower stage of ROP be defined as the treatment threshold [14, 20, 21]. In our series, in eyes that were treated with coagulation, we observed complete vascularisation and regressed ROP earlier than in untreated eyes with stage 3 ROP below threshold. Therefore, there may be a temptation to treat these eyes so as to obtain earlier stabilisation. However, as pointed out in the 3.5-year outcome of the Cryo-ROP study [5], treated eyes may show reduced grating acuity although the structure of the posterior pole is normal. In our series, without treatment the retinal development in nearly all cases progressed to a normal fundus appearance. We do not perform coagulation therapy prior to threshold ROP except in eyes with zone 1 disease or very rapid progression of ROP.

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