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Prevention of blindness due to retinopathy of prematurity at Hospital de Clínicas de Porto Alegre, Brazil: incidence, risk factors, laser treatment and outcomes from 2002 to 2006

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Introduction: Retinopathy of prematurity (ROP) is a multifactorial disease and a leading cause of blindness in children.

Purposes: The objectives of this paper are to evaluate in a prospective study the incidence, risk factors, the rate of diode laser treatment and main outcomes, in all very low birth weight and extremely premature infants from the Hospital de Clínicas de Porto Alegre, Brazil, between October 2002 and May 2006, in a screening program according to the Brazilian recommendations.

Materials and Methods: A prospective cohort study was conducted on 290 premature children with birth weight equal to or less than 1500 g or a gestational age at birth of 32 weeks or less. All of the newborns were examined by indirect binocular ophthalmoscopy with the 28 diopters lens after pupil dilatation and a lid speculum after 6 weeks of life and then repeated depending on the disease classification. The main risk factors included in this study were: use of mechanical ventilation, intraventricular hemorrhage, sepsis, APGAR index at 5 minutes, indomethacin and surfactant use, low weight gain at 6th week and blood transfusions.

Results: ROP occurred in 70 infants in a percentage of 25.7%. After logistic regression, it has been confirmed that the development of the disease is inversely proportional to the birth weight and gestational age at birth. The oxygen-therapy in mechanical ventilation, the use of surfactant and the low weight gain at the 6th week of life were all risk factors independent of the birth weight and gestational age. Threshold disease occurred in 4.48% of the cases (13/290). All of them had the disease affecting Zones III and II, and needed diode laser treatment under general anesthesia. Three of the treated children needed a second laser session. Only one premature developed the disease up to stage 5 of ROP resulting in a 0.34% of blindness due to the ROP at this institution in this period.

Conclusions: The incidence of ROP was similar to international results with the same profile as was also the percentage of 4.48% of threshold disease. The ophthalmologic examination at the 6th week of life is an important instrument for the detection of ROP and must be done in all very low birth weight infants and extremely premature infants specially. This study demonstrated the efficacy of the blindness prevention program for ROP employed at this hospital since October of 2002.

Key words: prematurity, retinopathy of prematurity, epidemiology, risk factors

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INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of blindness in children. It is a multifactorial disease affecting the development of the retinal vessels, occurring most frequently in the smallest and sickest infants. ROP is under constant study around the world due to the increasing survival of newborns of preterm delivery, within the groups of greater risk for the appearance of this disease: very low birth weight (BW) and extremely premature infants. In the more recent years, the survival rate in the extreme prematurity group of patients increased from 8% to 35% in the middle-income countries (1–5).

In Brazil, the 1st Workshop for the Study of ROP was held in Rio de Janeiro in October 2002, sponsored by the Brazilian Council of Ophthalmology and Brazilian Society of Pediatrics (6). At this time, certain decisions were taken in order to achieve a better understanding of the incidence of ROP in Brazil and to reduce the number of cases of blindness by adequate prevention and early treatment whenever necessary. The Hospital de Clķnicas de Porto Alegre (HCPA) implemented a screening project according to the standards defined for Brazil, which recommend binocular indirect ophthalmoscopy examination under dilation of pupils in all neonates with a BW equal to or less than 1500 g or with a gestational age (GA) equal to or less than 32 weeks at birth after the 6th week of life (6).

The objectives of this study are to evaluate the incidence of ROP among very low BW and among extremely premature infants, the significance of the postnatal risk factors and to assess whether these factors are independent of the two major risk factors, BW and GA at birth, the rate of treatment by transpupillary diode laser and the main outcomes in very low BW infants from the HCPA – Brazil between October 2002 and May 2006, in a screening program established to prevent blindness due to ROP, according to the Brazilian recommendations.

MATERIALS AND METHODS

A prospective cohort study of all very low BW infants born at the HCPA from October 2002 to May 2006 was done. All neonates that met the recommended criteria for screening ROP in Brazil, BW = 1500 g or GA = 32 weeks at birth, were included, except for those infants that died during hospitalization before the 6th week of life, i. e. the moment of the initial ophthalmological examination, which were excluded from this study. The main clinical outcome was the occurrence of any stage of ROP.

Main variables

To analyze the risk factors, gender, BW, GA (Ballard method), APGAR index at 5th minute, presence of intraventricular hemorrhage (IVH), use of oxygen in mechanical ventilation (MV), presence of sepsis and meningitis, the low weight gain at the 6th week of life (defined as a gain of weight from birth to the 6th week of life less than half of the birth weight), and the use of surfactant and indomethacin were included. All data referring to the risk factors were collected by the authors (JBFF, VLL, GUE).

Statistical analysis

Univariate and multivariate analyses were used to compare the risk factor variables in the study. Data were described by mean and standard deviation, and the significance level used was $\mu < 0.05$. To evaluate the strength of the correlations among the variables, odds ratios (OR) and confidence intervals (CI) were computed. All data were processed in the SPSS 13.0 (Statistical Package for Social Sciences) software.

Eye Examination Methods

All the exams were held at the HCPA Neonatology Center. The ophthalmologic exam consisted of the external inspection of the eyeballs and binocular indirect ophthalmoscopy with a 28 diopters Nikon lens (Melville, NY, USA) and the lid speculum for newborns developed by Storz (Alfonso Eye Speculum, Bausch & Lomb Inc., San Dimas, CA, USA), after the dilation of the pupils with association of the eye drops tropicamide 0.5% and phenylephrine 2.5%. Infants were first examined after the 6th week of life with retinal mapping and staging of retinopathy according to the International Classification of Retinopathy of Prematurity from 1984/1987 (7–9), and then followed depending on the severity of the disease, until retinal vascularization was completed. All ophthalmological examinations were done by the authors (JBFF, GUE).

Diode laser treatment

The diode laser FTC 2500 Diode Laser, 810 nm (Opto, Sao Carlos SP, Brazil) was used in all patients reaching the threshold disease. Treatment was done with transpupillary photocoagulation with binocular indirect ophthalmoscopy under general anesthesia. Both eyes were treated in the same time. All laser treatments were done by the same author (JBFF).

Outcome analysis

A 6-month follow-up study was performed, including the 67 prematures screened that presented for the follow-up appointment regularly until the 6 months of corrected age. All the patients were examined for presumed visual acuity, exam of the eye motility and alignment, cycloplegic refraction, indirect ophthalmoscopy and retinal mapping. Cycloplegic streak retinoscopy and fundus examination were carried out 30 minutes after the instillation of cyclopentolate 1%, phenilephrine 2.5% and tropicamide 0.5%, two drops each. Refraction was performed using handheld lenses in front of awake infants. All data from the outcomes were collected by the author (GUE).

RESULTS

Incidence of ROP among very low BW and extremely premature infants

From the group of 290 very low BW studied, ROP was identified in 24.14% of the cases. The disease reached stage 1 in 11.03%, stage 2 in 7.93% and stage 3 in 4.48% of the patients. Only one child from the group developed stage 5 of ROP with a severe loss of vision in both eyes (0.34%).

From the group of 55 patients with GA under 28 weeks or BW under 1000 g (extremely premature group), ROP was identified in 23 newborns (41.82%). These data are shown in Table 1.

Table 1. **Incidence of ROP in very low BW and extremely premature groups**

	290 very low BW prematures n (%)	55 extremely prematures n (%)
Newborns without ROP	220 (75.86)	32 (58.18)
ROP 1	32 (11.03)	7 (12.73)
ROP 2	23 (7.93)	10 (18.18)
ROP 3	13 (4.48)	6 (10.91)
ROP 4	1 (0.34)	0 (0)
ROP 5	1 (0.34)	0 (0)
Total of ROP	70 (24.14)	23 (41.82)

Risk factors for ROP

On univariate and multivariate analysis, indomethacin use, low weight gain, IVH, APGAR index less than 5 at five minutes and MV were considered significantly correlated with the development of the disease. After logistic regression, this study confirmed that the development of the disease is inversely proportional to BW and GA at birth. The use of the oxygen-therapy in MV, the use of surfactant and the low weight gain at the 6th week of life were considered risk factors independently of the BW and GA (Tables 2, 3 and 4).

Transpupillary diode laser treatment for ROP

Threshold disease was reached in only 4.48% (13/290). All threshold diseases were in Zones II or III, none in Zone I. The mean BW of the treated group was 964.29 g and the mean GA was 28.79 weeks. A transpupillary diode laser was used in all of these patients. Both eyes were treated in the same time, under general anesthesia in the surgical room. Confluent laser spots, around 800 in each eye, were used for all children, without any complications of the laser treatment. Three patients needed a second laser treatment in both eyes, four weeks after the initial treatment. One patient of the re-treated group needed scleral buckling with an equatorial silicon band after progression for stage 4 of ROP. The anatomical outcome was good in all neonates (Table 5).

Table 2. **Risk Factors and ROP**

Risk factors	Group 1*	Group 2*	P	OR	CI 95%
Female Gender	44 (28.0)	25 (20.5)	0.16	1.51	0.86–2.64
Use of O_2 in MV	58 (42.6)	11 (7.9)	<0.001	8.72	4.31–17.61
IVH	17 (38.6)	52 (22)	0.02	2.23	1.12–4.40
Indomethacin	37 (41.1)	32 (17.1)	<0.001	3.38	1.91–5.96
Low Weight Gain	43 (40.6)	25 (16.2)	<0.001	3.52	1.97–6.27
Surfactant	56 (41.8)	13 (9.2)	<0.001	7.12	3.66–13.86
Sepsis	62 (30.2)	7 (9.9)	<0.001	3.96	1.71–9.13
Blood Transfusions	50 (39.4)	19 (12.8)	<0.001	4.44	2.44–8.08
Meningitis	13 (52)	56 (22.3)	0.003	3.77	1.63–8.72

* Group 1 – with the risk factor, group 2 – without the risk factor. Data in n (%).

Table 3. **Risk factors and ROP***

Risk factors	ROP	Without ROP	P
Birth weight	1050.87 ± 274.72	1258.67 ± 273.56	<0.001
Low weight gain	454.78 ± 216.60	679.16 ± 278.61	<0.001
Gestational age	29.32 ± 2.17	30.71 ± 2.18	<0.001
Apgar index 5'	7.49 ± 1.73	8.07 ± 1.52	0.009

* Data with mean ± standard deviation.

Table 4. **Risk factors – odds ratio (OR) adjusted for the main risk factors**

Risk factors	OR	IC 95%	P
Use of O_2 in MV	4.38	1.95–9.85	<0.001
Use of surfactant	4.50	2.03–9.98	<0.001
Low weight gain	4.20	2.12–8.35	<0.001

Table 5. **BW and GA at birth of 13 patients treated by laser photocoagulation**

Case	BW	GA	Nº sessions
1	990	29	1
2	710	26	1
3	635	27	1
4	780	31	2
5	625	26	2
6	1230	31	1
7	620	25	1
8	1315	33	1
9	1080	26	1
10	1500	30	1
11	920	30	2
12	1260	28	1
13	900	31	1
Mean	964.29	28.79	
Median	927.5	29.5	
Std. deviation	281.44	2.46	
Minimum	620	25	
Maximum	1500	33	

Outcomes after 6-month follow-up

Sixty seven patients (134 eyes) were studied. Twenty five (37.31%) developed ROP at any stage and seven needed laser treatment for threshold disease. Mean GA for the ROP group was 29.47 weeks (range 25–36 weeks), versus 31.9 weeks (range 27–34 weeks) for the non-ROP group. At 6 months of corrected age, patients who developed ROP were significantly more myopic (9 patients, 36%) than those who didn't (2 patients, 4.7%). Otherwise, non-ROP patients were significantly more hyperopic (37 patients, 88%) than the ROP group (16 patients, 64%). Astigmatism presented in 20 (80%) of the ROP patients and in 25 (59.5%) of the non-ROP infants. Among the patients who underwent laser therapy, 57.14% developed myopia. On the other hand, only 27.7% of the patients in the ROP group without laser therapy developed myopia. Strabismus was detected in 3 patients in the ROP group and 2 in the non-ROP group. Retinal changes were diagnosed just in the ROP group. Fundus abnormalities included macular changes in one patient, Zone II retinal scars in one patient, peripheral retinal scars in 6 patients and pale optic disc in one patient (Table 6).

Table 6. **Six-month outcomes in 67 patients**

	ROP group	Non-ROP group
Mean GA (range)	29.47 (25–36)	31.9 (27–34)
Myopia	9 (36%)	2 (4.7%)
Hyperopia	16 (64%)	37 (88%)
Astigmatism	20 (80%)	25 (59.5%)
Strabismus	3 (12%)	2 (4.7%)

DISCUSSION

Retinopathy of prematurity was first reported in 1942 by Terry, who published a description of the histological findings of what would now be considered end-stage cicatricial disease (10; 11). In its advanced forms, it can result in severe visual impairment or blindness, affecting the normal motor, language, conceptual, and social development of the child and having a high financial cost for the community (12).

Incidence of ROP

Programs for the prevention of blindness from ROP were initiated in many countries beginning in the 80s when the Cryotherapy for Retinopathy of Prematurity Cooperative Group (Cryo-ROP) demonstrated the first positive results from the treatment of this disease with cryotherapy (13–18). The study carried out in the USA from January 1986 to November 1987 evaluated 4099 children born with less than 1251 g in order to monitor the incidence and evolution of the disease. This large study set the incidence of ROP in some degree at 65.8% considering all patients and in 81.6% considering all children born with less than 1000 g (19).

Larsson and Holmström published the development of ROP in 25.5% of the 392 children prospectively studied in Stockholm, Sweden between 1998 and 2000 and also the appearance of stage 3 of ROP in 11.7% (46/392) (20). Also in Europe, a retrospective study was published in 2002 about 194 children born prematurely with less than 1500 g or with less than 32 weeks of GA during a period of 9 years from 1992 to 2000. In this population, stages 1 and 2 occurred in 26.28% (51/194) and only 2.5% of those examined (5/194) needed cryotherapy (21).

At John Dempsey Hospital from the University of Connecticut School of Medicine, USA, between 1989 and 1997, data on 950 newborns were evaluated retrospectively. The authors obtained 21.3% of ROP (202/950) considering all stages, and only 4.6% (44/950) of the children examined reached stage 3 or more of ROP. This study also determined that none of the children born with more than 1000 g or with more than 28 weeks of GA developed stages of ROP that would need intervention by laser or by surgery (22).

In Brazil, the study by Graziano et al. published in 1997 analyzed retrospectively data on 102 premature infants born with less than 1500 g from January 1992 to December 1993 and detected a percentage of 29.09% of ROP including all stages. This work stands out due to the very high prevalence of ROP (78.5%) in the group of patients with BW less than 1000 g and 72.73% in infants born with GA of less than 30 weeks. The authors have concluded that children of lower BW or GA (below 1000 g or below 28 weeks) are at a greater risk of developing ROP in stage 3 or more (23).

Our findings are important because they confirmed the high incidence of ROP (41.82%) and threshold disease (10.91%) in the extremely premature group.

Risk factors

The modern concept of ROP defines it as a multifactorial disease directly related with the level of immaturity of each child, which means that the lower GA results in a lower BW and a greater probability of retinopathy taking place. Although many factors were identified and proposed to explain ROP development, only low BW, low GA and long-time oxygen-therapy following delivery have been consistently associated with this disease (12).

In the present study, supported by data collected from 290 neonates a high importance of low weight gain at the 6th week of life was noted as a risk factor independent of the BW and of GA, participating in the development of ROP (OR 4.20; CI 2.12–8.35; $p < 0.001$). This important statement was suggested before by Wallace in 2000 (24) and also by Allegaert in 2003 (25), and was confirmed by our results. Using stepwise logistic regression, our study also confirmed that the ROP group had a statistically significantly lower birth weight, younger GA, and the use of surfactant and oxygen-therapy in mechanical ventilation.

Laser treatment

In the management of ROP, several studies have demonstrated laser photocoagulation to be as effective as cryotherapy in reducing the incidence of unfavourable structural outcome and nowadays most of the specialized centers in the treatment of ROP use the transpupillary photocoagulation by argon or diode laser applied by binocular indirect ophthalmoscopy as the best of the alternatives for treatment.

In the present study, 13 patients with threshold disease were considered for treatment with transpupillary diode laser, with approximately 800 confluent spots at the peripheral avascular retina in each eye. The anatomical outcome was good in all neonates, despite that in 23.07% laser re-treatment was required to stabilize the disease. Some reasons for this high re-treatment level in Zone II threshold disease could be explained by the low number of laser spots applied to each eye.

Bannach in 2000 and Rezai in 2005, published that the near confluent pattern of laser photocoagulation may reduce the rate of progression of threshold retinopathy of prematurity in Zone II. The near confluent pattern with approximately 1200 laser spots may also reduce the re-treatment rate of the disease, but larger studies are needed to confirm these findings (26).

McNamara et al. (27) analyzed in 1993 the complications of laser photocoagulation treatment in ROP and showed mainly complications restricted to the anterior segment, as corneal edema, iris damage, lens damage and cataract formation. Most of the related complications at the anterior segment were observed after argon laser therapy and none with diode laser therapy. Retinal and choroidal hemorrhages, choroidal neovascularization, epi-retinal membrane formation and later retinal detachment were the main complications associated with the diode laser treatment for ROP. None of the 13 patients treated in the HCPA showed any of these complications.

The objective of the systemic care of newborns in the risk group for the development of ROP is to determine the adequate moment for treatment. In our study all neonates were treated in threshold disease once, classically, the threshold disease is considered the right moment to treat, but recently, the results of the Early Treatment for ROP Cooperative Group have shown that treatments at the prethreshold disease significantly reduce unfavorable outcomes in both primary and secondary (structural) measures. This can induce the clinicians all over the world to treat at the prethreshold disease (28).

Outcomes

This Brazilian study suggests a higher risk for myopia (especially in the ROP group that was submitted to retinal photocoagulation) and retinal changes among patients treated after developed ROP. The association between myopia and ROP has been recognized for many years occurring mainly after cryotherapy but also after the laser photocoagulation in spite of the laser produces less myopic shift (29).

The results here presented in threshold disease are in agreement with other studies published in the literature in spite of the paper from Davitt et al. from the Early Treatment for ROP Cooperative Group that demonstrated that the early treatment at a high-risk prethreshold did not raise the risk of developing myopia compared with conventional management. Previous results from the multicenter study of Cryotherapy for ROP (Cryo-ROP) demonstrated that anisometropia, astigmatism, and presence of posterior pole residua from ROP are associated with higher incidence of myopia and high myopia (= 5.0 D). However, when results from treated versus control eyes were compared, there was little change in the distribution of the refractive error in treated or control eyes between 1 year and 10 years of age (29, 30).

The aetiology of myopia among prematures with ROP is still controversial and unknown, needing furthers researches into this subject to be understood if is the myopia due to the disease or to the treatment?

CONCLUSIONS

The incidence of 24.14% of ROP found in this study was similar to data reported by other authors with a similar design as well as with the percentage of those needing treatment. The authors call attention to the higher incidence of ROP among the extremely premature infants, in which ROP incidence increased to 41.82% considering all stages.

In the group of thirteen neonates that reached threshold disease, the transpupillary diode laser was effective to stop the natural progression of the disease in spite of one patient of the treated group needed scleral buckling with an equatorial silicon band after progression for stage 4 of ROP.

In the study here presented, supported by the data collected from 290 neonates, was noted the high importance of the low weight gain at the 6th week of life as an risk factor independent from the BW and also from the GA, participating in the development of ROP.

This study also suggests a higher risk for myopia (especially on ROP group that was submitted to retinal photocoagulation) and retinal changes among patients that developed ROP. The results are in agreement with other studies published in the literature.

Only one case of stage 5 of ROP occurred during the study period, in a percentage of 0.34%, thus showing the efficacy of the prevention program of blindness due to ROP implemented in this hospital since October 2002.

The Brazilian screening for ROP implanted after the 1st Workshop RJ 2002 was effective to detect all the cases of threshold disease needing laser treatment and prevented blindness in 13 neonates in this period. The widespreading of the screening criteria could prevent one of the leading causes of childhood blindness.

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