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The prevalence of retinopathy of prematurity in very low birth weight newborn infants

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Abstract

Objective: To evaluate the prevalence of retinopathy of prematurity and the risk factors affecting very low birth weight infants at a neonatal intensive care unit.

Methods: A cross-sectional study investigating all newborn infants with birth weights ≤ 1,500 g and/or gestational ages ≤ 32 weeks, admitted to the Neonatal ICU at the *Hospital de Clínicas de Porto Alegre*, from October 2002 to March 2004. Patients underwent indirect binocular ophthalmoscopy of the fundus at six weeks postpartum. Infants who progressed to threshold disease were given laser therapy.

Results: One hundred and fourteen newborn infants were studied. Eighty-three patients were not diagnosed with retinopathy of prematurity, 18 had stage I retinopathy of prematurity, seven stage II retinopathy of prematurity and six patients had threshold retinopathy of prematurity. The prevalence of retinopathy of prematurity was 27.2% (95% CI: 19.28-36.32) affecting 31 newborn infants, and the prevalence of retinopathy of prematurity progressing to threshold disease was 5.26% (95% CI: 1.96-11.10), affecting six patients. Retinopathy of prematurity was confirmed in 50% of the patients with weights below 1,000 g and 71.5% of newborn infants born at gestational ages of less than 28 weeks. Gestational age and birth weight were significantly lower among patients with retinopathy of prematurity than among those without.

Conclusions: Although the results of this study demonstrate that the observed prevalence was similar to that described in literature, this ROP frequency remains elevated among very low birth weight infants. The development of retinopathy of prematurity was inversely proportional to weight and gestational age at birth.

J Pediatr (Rio J). 2006;82(1):27-32: Blindness, retinopathy, very low weight, oxygen therapy, risk factors.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative ocular disease of multi-factor etiology, secondary to inadequate retinal vascularization.[1]

In the USA ROP is the second most common cause of blindness among children less than 6 years old and it is estimated that of the 100,000 blind Latin American children, 24,000 are blind because of ROP.[2]

Early identification of retina damage and the institution of appropriate treatment prevent blindness and offer children better overall development.[3]

The American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Ophthalmology recommend the ophthalmological examination of premature newborn infants with birth weights less than or equal to 1,500 g and gestational ages less than or equal to 28 weeks when they reach six weeks postpartum.[4] According to the Brazilian Ophthalmology Council (*Conselho Brasileiro de Oftalmologia*), the Brazilian Pediatric Ophthalmology Society (*Sociedade Brasileira de Oftalmologia Pediatrica*) and the Brazilian Society of Pediatrics (*Sociedade Brasileira de Pediatria*) ophthalmological examination is indicated for premature newborn infants born weighing 1,500 g or less and at gestational ages of 32 weeks or less.[5,6] Fundus examinations are performed with an indirect binocular ophthalmoscope after adequate dilation of the pupils.

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Treatment at the correct time with laser photocoagulation can avert disease progression and the irreversible blindness that results.[3]

In Brazil, the Health Ministry does not have exact figures for the number of children affected by ROP, but it is estimated that around 16,000 newborn infants develop ROP annually and approximately 1,600 of these will become blind if not detected and treated promptly. Studies of the prevalence of ROP and assessments of ROP derived blindness prevention programs are important to Brazil.[5,7]

The objective of this study was to evaluate the prevalence of ROP in very low birth weight infants at the neonatal intensive care unit of the *Hospital de Clínicas de Porto Alegre* and also to analyze possible risk factors associated with ROP in this population.

Patients and methods

An observational cross-sectional study was performed that included all the newborn infants with birth weights less than or equal to 1,500 g and/or gestational ages at birth of 32 weeks or less seen at the Neonatology Service at the *Hospital de Clínicas de Porto Alegre*, from 1 October 2002 to 31 March 2004. Newborns who died before completing 6 weeks were excluded.

All medical procedures undergone, all medication received and all intercurrent conditions suffered by the infants were recorded. The indirect binocular ophthalmological examination was performed for all patients at six weeks postpartum after adequate dilation of the pupils with a combination of eye drops containing tropicamide 0.5% and phenylephrine 2.5%, one drop every 10 minutes, three times, approximately one hour prior to the examination. A 28 diopter lens with a blepharostat for newborns by Storz was employed in order to provide sufficient view of the extreme periphery of the retina through 360° without routine scleral depression. All ophthalmologic examinations were performed by the same ophthalmologist at the neonatology center and with no prior knowledge of the patients' medical histories.

Retinopathy of prematurity staging was defined according to the International ROP classification which classifies disease progression according to the following findings:[8]

Stage 1: peripheral ischemia of the retina and a demarcation line between the vascular and avascular regions of the retina;

Stage 2: presence of an elevated ridge in the periphery of the retina;

Stage 3: retinal or extraretinal fibrovascular proliferation (neovascularization) present on the ridge;

Stage 4: subtotal retinal detachment beginning at the ridge, either without fovea involvement (4A), or with involvement of the fovea (4B);

Stage 5: total retinal detachment;

Threshold disease: stage 3 ROP , in zones 1 or 2 , with at least 5 contiguous or 8 noncontiguous hours and plus disease (dilation and tortuosity of the peripheral retinal vessels, iris vascular engorgement, pupillary rigidity, and vitreous haze)

Pre-threshold disease type 1: zone 1 at any stage with plus disease or zone 1 at stage 3 without plus or zone 2 at stages 2 or 3 with plus.

Pre-threshold disease type 2: zone 1 at stages 1 or 2 without plus or zone 2 at stage 3 without plus.

The ROP classification was revised recently, but it was published after our study had been performed and so could not be employed here.

All patients who progressed to threshold disease received laser photocoagulation treatment.[10] All infants were followed-up at outpatients appointments from hospital discharge until involution of retinopathy or complete retinal vascularization of the retina. After each examination a datasheet was filled out containing maternal parameters, infant variables and information on the delivery, for purposes of later comparison between outcome groups.

The variables studied were sex, birth weight, gestational age, fifth minute Apgar score, nutritional status at birth according to the Alexander et al.[11] intrauterine growth curve in addition to the use of supplementary oxygen, mechanical ventilation, intracranial hemorrhage, prophylactic and/or therapeutic indomethacin and blood transfusions.

Gestational age was estimated according to maternal history, obstetric echography if taken during the first trimester of pregnancy and was confirmed by physical examination of the newborns themselves.

All of the newborn infants were examined by fontanelle ultrasound at the end of the first week postpartum for diagnosis of intracranial hemorrhages.

The prevalence rate of ROP was calculated for the whole study population and then stratified by $\leq$ 1,000 g birth weight and by $\leq$ 28 weeks' gestational age.

Sample size was estimated at 115 patients to obtain a ROP prevalence estimate with a margin of error of up to 1% and a 95% confidence interval ($\alpha = 0.05$).

Quantitative parametric data are described in the form of means and their standard deviations and categorical variables are expressed in percentages and frequencies. The prevalence rates of retinopathy of prematurity are described in simple proportions with their 95% confidence intervals determined by binomial distribution. Quantitative variables were compared with Student's t test for two independent samples or, in cases where three or more possibilities existed, with analysis of variance (ANOVA), while the Tukey test was employed for multiple comparisons

between averages. Comparisons between categorical variables were made using the chi-square test or Fisher's exact test. The significance cutoff adopted was $\alpha = 0.05$.

Logistic regression analysis was performed for the dependent variable presence/absence of ROP with those independent variables that were biologically plausible and which had been shown to be significant in the univariate analysis.

This research was approved by the Healthcare Research and Ethics Commission at the HCPA and parents or guardians of all patients signed an Informed Consent Form.

Results

One hundred and thirty-nine newborn infants with birth weights less than or equal to 1,500 g and/or gestational ages of 32 weeks or less were admitted to the Neonatology Service at the HCPA during the study period. Twenty-two (15.82%) patients were excluded because they died before reaching 6 weeks and three patients were lost, with 114 patients making up the final study population. Table 1 presents the characteristics of the patients included in the study.

Table 1 - Characteristics of the patients included in the study

Variables	Descriptive measures
Female (%)	65 (57%)
Weight at birth (grams)	1,214.8±279.8
Gestational age (weeks)	30.5±1.8
Fifth minute Apgar	8±1.4
Oxygen (%)	105 (92.1%)
Mechanical ventilation (%)	63 (60%)
Intracranial hemorrhage (%)	25 (21.9%)
Prophylactic indomethacin (%)	15 (13.2%)
Therapeutic indomethacin (%)	19 (16.7%)
Blood transfusions (%)	51 (44.7%)
Classification, AGA (%)	72 (63.2%)

Data presented as frequency (%) or mean±standard deviation.
AGA = appropriate for gestational age.

Eighty-three (72.8%) infants were not diagnosed with ROP. The overall prevalence of ROP was 27.2% (95% CI: 19.28-36.32), affecting 31 newborn infants. The prevalence of threshold disease was 5.26% (95% CI: 1.96-11.10) affecting six patients. None of the infants presented ROP at stages 4 or 5. Fifty percent (n = 14) of the newborn infants with birth weights < 1,000 g were diagnosed with ROP and 19.8% (n = 17) of the newborn infants with birth weight $\geq$ 1,000 g ($p < 0.003$) had ROP, with three from each group requiring surgery. Retinopathy of prematurity was present in 71.5% (n = 5) of the patients with gestational age < 28 weeks and 24.3% (n = 26) of the newborn infants with gestational age $\geq$ 28 weeks ($p < 0.001$), with three from each group requiring surgery. All of the patients with and without ROP were followed until involution of retinopathy or complete retinal vascularization.

Table 2 demonstrates the comparison between the groups with and without ROP, with statistical significance in birth weight, gestational age, mechanical ventilation and blood transfusions. Table 3 demonstrates a comparison between patients without ROP and patients with ROP Stages 1, 2 and 3.

Those variables that were statistically significant after univariate analysis were analyzed using a logistic regression model, with weight and gestational age kept separate because of the existence of colinearity between them (Table 4). Low birth weight or gestational age remained the significant variable.

It was not possible to perform multivariate analysis after stratification due to the small number of patients in each group.

The six newborn infants with ROP that progressed to threshold disease required surgery. None of these six required any other treatment, but one of them did need laser photocoagulation to be repeated for both eyes. All of the newborn infants who were treated had both eyes treated on the same occasion.

Discussion

The first description of retina damage in premature newborn infants was published in 1945 by Terry who reported on 117 cases of blindness described as retrolental fibroplasia.[12] There have been two well-defined ROP epidemic phases: during the 50s, attributed to the extensive use of oxygen in neonatal ICUs and again during the seventies due to increased survival of extremely low weight premature newborn infants.[13]

In normal retina development vessels grow outwards from the optic disc to the ora serrata, from 16 weeks' gestational age onwards. The nasal ora serrata is reached at around 36 weeks' gestational age and the temporal ora serrata at around 40 weeks. Retinopathy of prematurity develops because of the cessation of vasculogenesis. Instead of a gradual transition from vascular to avascular regions, there is an abrupt limit to the vascular area marked by a demarcation line that indicates the onset of ROP.

The etiopathogenesis of ROP is related to oxygen-related and non-oxygen-regulated factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1), respectively.[1] Both of these inhibit retinal

Table 2 - Comparison of characteristics of patients with and without ROP

Variables	ROP n = 31	Without ROP n = 83	p
Weight at birth (g)	1,045±272	1,278±256	< 0.001
Gestational age (weeks)	29.1±1.4	31±1.7	< 0.001
Female (%)	21 (67.7%)	44 (53%)	0.203
Classification of nutritional status AGA (%)	15 (48.4%)	57 (68.7%)	0.053
Oxygen (%)	31 (100%)	74 (89.2%)	0.111
Mechanical ventilation (%)	27 (87.1%)	36 (43.4%)	< 0.001
Prophylactic indomethacin (%)	7 (22.6%)	8 (9.6%)	0.115
Therapeutic indomethacin (%)	9 (29%)	10 (12%)	0.046
Intracranial hemorrhage (%)	9 (29%)	16 (19.2%)	0.311
Blood transfusions (%)	23 (74.2%)	28 (33.7%)	< 0.001
Fifth minute Apgar	7.6±1.4	8.1±1.4	0.071

Qualitative variables with percentage were described and compared through Fisher's exact test.
Quantitative variables by mean and standard deviation were described and e compared through Student's *t* test for independent samples.
ROP = retinopathy of prematurity; AGA = appropriate for gestational age.

Table 3 - Characteristics of the groups included in the study according to the results of indirect binocular ophthalmoscopy

Variables	Without ROP n = 83	ROP 1 n = 18	ROP 2 n = 7	ROP threshold disease n = 6	p
Female (%)	44 (53%)	15 (83.3%)	5 (71.4%)	1 (16.7%)	0.017
Weight at birth (grams)	1,278±256[a]	1,150±225[a]	792±227[b]	1,025±283[a,b]	< 0,001
Gestational age (weeks)	31.0±1.7[a]	29.5±1.2[a]	28.1±1.5[b]	29.3±1.6[a,b]	< 0.001
Fifth minute Apgar	8.1±1.4	7.6±1.2	7.1±2.0	8.0±1.2	0.220
Oxygen (%)	74 (89.2%)	18 (100%)	7 (100%)	6 (100%)	0.302
Mechanical ventilation (%)	36 (43.4%)[a]	15(83.3%)[b]	7 (100%)[b]	5 (83.3%)[a,b]	0.022
Intracranial hemorrhage (%)	16 (19.2%)	4 (22.4%)	1 (14.3%)	4 (66.6%)	0.325
Prophylactic indomethacin (%)	8 (9.6%)	3 (16.7%)	3 (42.9%)	1 (16.7%)	0.087
Therapeutic indomethacin (%)	10 (12%)	5 (27.8%)	2 (28.6%)	2 (33.3%)	0.188
Blood transfusions (%)	28 (33.7%)[a]	11 (61.1%)[a,b]	6 (85.7%)[b]	6 (100%)[b]	< 0.001
Classification, AGA (%)	57 (68.7%)	11 (61.1%)	2 (28.6%)	2 (33.3%)	0.072

Qualitative variables with percentage were described and compared through the chi-square test. Quantitative variables by mean and standard deviation were described and compared through the ANOVA test. Tukey's test of multiple comparisons between means was performed.
[a,b] different letters represent different means with $p < 0.05$.
ROP = retinopathy of prematurity; AGA = appropriate for gestational age.

vascularization in small quantities and predispose to neovascularization when present in excessive quantities. Hyperoxia after the birth of premature newborns inhibits the production of VEGF, and maintaining supplementary oxygen during the neonatal period leads to overproduction of VEGF, stimulating neovascularization of the retina. Insulin-like growth factor has a role in normal retinal

Table 4 - Logistic regression model

Variables	OR	95% CI	p
Gestational age	0.633	0.453-0.886	0.008
Mechanical ventilation	3.474	0.997-12.107	0.051
Blood transfusions	1.978	0.675-5.792	0.213

development. Newborn infants with ROP exhibit lower serum IGF-1 levels than controls with 33 weeks' postconceptional age and this finding is predictive of ROP.[14]

Other risk factors for ROP have been identified in literature include septicemia, congenital infections, ventilatory support, blood transfusions, intracranial hemorrhage , asphyxia and vitamin E deficiency.[6]

Studies of the prevalence of ROP have found values similar to those found in our study.

Reisner et al. studied 1,070 newborn infants, observing a 20% prevalence of ROP among newborn infants weighing less than 2,500 g, 21% for those below 1,500 g, 35% for weights under 1,250 g and 72% for babies born weighing less than 1,000 g. Threshold disease was found in 9% of the newborn infants with weights below 1,500 g.[15]

A multicenter study of cryotherapy for ROP (CRYO-ROP) undertaken in the United States from January 1986 to November 1987 assessed 4,099 newborn infants with birth weights below 1,251 g in order to monitor the incidence and course of the disease. The prevalence of ROP in that study was 65.8% for the whole group and 81.6% at weights below 1,000 g.[16]

In 1991, Charles et al. reported a prevalence of ROP of 72% among newborn infants weighing less than 1,200 g and of 66% for newborn infants born at less than 32 weeks' gestational age.[17]

Purohit et al. studied 3,025 newborn infants in a multicenter study in the USA from 1979 to 1981 and found a prevalence of ROP of 11% for weights below 1,750 g and 43% for birth weights below 750 g.[18]

Robinson & O'Keefe reported a prevalence rate of ROP of 47% for newborn infants with weights from 1,000 g to 1,500 g, and of 49% for newborn infants with gestational ages from 28 to 32 weeks.[19]

In Brazil, Graziano et al. prospectively analyzed 102 newborn infants with birth weights below 1,500 g between 1992 and 1993, detecting an overall ROP prevalence rate of 29.09% and threshold disease prevalence of 3%.[20]

Hussain et al. studied 950 newborn infants and observed an ROP prevalence of 21.3% and 4.6% of Stage 3 or higher ROP. They studied newborn infants born at less than 30 weeks or weighing less than 1,300 g, newborn infants less than 35 weeks or with weights less than 1,800 g and given oxygen for more than 1 week and any newborn given oxygen for more than 60 days. The same study showed that no infant born weighing more than 1,000 g and at more than 28 weeks' gestational age developed stage 3 or higher ROP.[21]

Larsson et al. studied 392 newborn infants from 1998 to 2000, in Stokholm, Sweden. In 2002 they published a prevalence rate of 25.5% of ROP overall and a prevalence of 11.7% of ROP with threshold disease.[22]

Asproudis et al. assessed 194 newborn infants smaller than 1,500 g or 32 weeks' gestational age. The prevalence of ROP at stages 1 and 2 was 26.28% and for ROP with threshold disease it was 2.5%.[23]

Chiang et al., in New York State, assessed 15,691 newborn infants between 1996 and 2000, broken down by weight range. All of the patients born during the period were included. The prevalence of ROP at < 1,500 g was 20.3%, at < 1,200 g it was 27.3% and at below 1,000 g it was 33.2%. The prevalence of ROP with threshold disease was 9.5%.[24]

Published data demonstrate that ROP is primarily linked with low gestational age and birth weight.[16,20,24] After logistic regression analysis, our study confirmed that these are the significant risk factors for ROP in our study population. The other risk factors for ROP were not significant in our study, after analysis by logistic regression. Analysis of risk factors by birth weight (< 1,000 g and $\geq$ 1,000 g) or gestational age (< 28 weeks and $\geq$ 28 weeks) was not carried out because the sample size was insufficient for multivariate analysis. We should bear in mind that the original sample size was calculated to investigate the prevalence of ROP in very low birth weight infants. For the analysis of relationships the sample size was too small, but it serves to suggest some possible associations.

In common with what has been described in literature, 66.7% of the patients in our sample who progressed to threshold disease were small for gestational age.[19]

Programs for the prevention of ROP-derived blindness have shown positive results from the treatment of the disease.[3] The objective of systematically screening the high-risk portion of newborn infants for the appearance of ROP is to determine the correct moment for laser photocoagulation treatment in order to prevent blindness.

Considering the results returned by this study, we can conclude that the prevalence observed here is close to figures in published literature. The development of ROP was inversely proportional to weight and gestational age at birth.

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