Prevalence of retinopathy of prematurity: an institutional cross-sectional study of preterm infants in Brazil

João B. Fortes Filho,1 Gabriela U. Eckert,2 Fabiana B. Valiatti,2 Marlene C. da Costa,3 Pedro P. Bonomo,4 and Renato S. Procianoy5

Objective. Retinopathy of prematurity (ROP) is the leading cause of childhood blindness in most developed countries. This study aimed to verify ROP prevalence among all very low birth weight (VLBW) preterm infants admitted to a level-3 teaching hospital in Porto Alegre, Rio Grande do Sul, Brazil.

Methods. Institutional cross-sectional study of 407 premature infants with birth weight ≤1 500 g or gestational age (GA) ≤32 weeks between 2002 and 2007. All infants screened for ROP were examined after the fourth week of life and followed up until the 45th week of adjusted GA. ROP prevalence was estimated at a 95% confidence level.

Results. Some degree of ROP in one or both eyes occurred in 25.5% (104) of all screened infants, and severe ROP (threshold stage 3 or higher, requiring treatment to prevent vision loss, as per the criteria of the U.S.-based Multicenter Trial of Cryotherapy for Retinopathy of Prematurity, CRYO-ROP) occurred in 5.8% (24). Based on the criteria of The International Classification for Retinopathy of Prematurity (ICROP, 1984/1987), the disease reached stages 1, 2, and 3 in 11.3% (46), 8.4% (34), and 5.4% (22), respectively. One infant developed the disease up to stage 4 (partial retinal detachment), and one progressed to stage 5 (complete retinal detachment, resulting in 0.2% overall prevalence for ROP-induced blindness).

Conclusions. Overall incidence of ROP in this institutional study (25.5%) was comparable to international results from developed countries. A comprehensive countrywide survey on ROP in Brazil is recommended to determine any regional differences in disease prevalence.

Key words Blindness, prevention & control; retinopathy of prematurity, epidemiology; prevalence; Brazil.

Retinopathy of prematurity (ROP) is a blinding disease in children occurring most often among preterm newborns of low birth weight (BW) or low gestational age (GA) (time elapsed between first day of last normal menstrual period and day of delivery, expressed in complete weeks) (1). ROP is one of the most important causes of treatable childhood blindness in industrialized countries and is becoming increasingly prevalent in middle-income Latin American countries such as Brazil (2, 3).

ROP is under constant epidemiological study around the world due to the higher survival rates of very low birth weight (VLBW) preterm infants (preterm neonates with BW ≤1 500 g), according to reports from many Latin American countries (4–6). This same situation seems
to occur in Eastern Europe as well as in some Asian countries (e.g., India) once progress in science and technology has permitted improvement in neonatal care of preterm infants (7, 8).

In Brazil, it is estimated that each year about 15 000 surviving preterm infants at risk for developing ROP require screening examinations for diagnosis. Without treatment, an average of 562 children from this at-risk population are expected to go blind each year, resulting in a high socioeconomic cost, especially for a disease that is both preventable and treatable (9). Brazilian guidelines for neonatal screening for ROP were established in October 2002, during the first ROP Workshop (1° Workshop de Retinopatía da Prematuridade) in Rio de Janeiro. This national meeting aimed to increase understanding about the prevalence of this disease in Brazil and to lower the number of cases of ROP-induced blindness quickly through adequate prevention and, when necessary, treatment (provided early in the course of the disease). The published guidelines for ROP screening for most Brazilian regions call for ophthalmological examinations of all preterm infants with BW ≤1 500 g or GA ≤32 weeks, initiated between the fourth and sixth week of life. The guidelines also call for screening of neonates in critical clinical conditions (as determined by the attending neonatologist), including those outside the population deemed at risk for ROP (10).

In 2002, the Clinics Hospital of Porto Alegre (Hospital de Clínicas de Porto Alegre, HCPA), a level-3 teaching hospital at Federal University of Rio Grande do Sul in Porto Alegre, a city of 3 million in Brazil’s southernmost state, Rio Grande do Sul, implemented a screening program for diagnosis of ROP based on the Brazilian national guidelines. This study aimed to determine the prevalence of ROP among 407 VLBW infants admitted to HCPA’s Neonatal Intensive Care Unit (NICU) and screened for ROP.

**MATERIALS AND METHODS**

The current study was cross-sectional and based on institutional data from a cohort of 407 preterm infants prospectively followed from 4 to 6 weeks after birth to the end of the first year of life. The ROP diagnosis was based on a cross-sectional search conducted during the 45th week of adjusted GA (chronological age reduced by number of weeks born before 40 weeks of gestation).

The study included all VLBW preterm infants admitted to HCPA between October 2002 and December 2007 who survived through the 45th week of adjusted GA (i.e., infants who died during hospitalization before the initial ophthalmological examination, and those who died before the 45th week of adjusted GA, were excluded). The VLBW group comprised infants with BW ≤1 500 g and, as per Brazilian guidelines for ROP screening, infants with BW >1 500 g but with GA ≤32 weeks.

The main study outcomes were 1) occurrence of ROP in any of its five stages of development and 2) occurrence of severe ROP (requiring treatment to prevent vision loss) in one or both eyes during the observation period (from 4–6 weeks after birth through the 45th week of adjusted GA). The worst stage of ROP, in either eye, was recorded. The ROP was classified by location (on the retina) (zone 1–3), and severity (stage 1–5), according to the criteria of the U.S.-based Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) (13) (five or more contiguous or eight cumulative clock hours (30-degree sectors) of stage 3 in either zone I or II with plus disease (dilation and tortuosity of the posterior retinal blood vessels)).

The 407 infants in the study cohort were divided into the following four patient groups: Group 1, the entire cohort of screened infants; Group 2, infants with BW ≤1 000 g; Group 3, infants with BW >1 000 g and ≤1 250 g; and Group 4, all infants with BW >1 250 g. The absolute and relative frequencies of ROP were estimated with a 95% confidence interval (CI), and the mean and standard deviation (SD) were calculated for the continuous variables (BW and GA).

The sample size was determined according to data in the Brazilian scientific literature that estimate about 25–30% of VLBW premature infants will have some degree of ROP, requiring a minimum of 323 patients for estimating ROP prevalence with a 95% CI and a maximum acceptable difference of 5% (14).

All examinations were performed at the HCPA NICU between October 2002 and December 2007. The infants were examined while hospitalized and as outpatients (after discharge) up to the 45th week of adjusted GA. The ophthalmological exam consisted of binocular indirect ophthalmoscopy with a 28-diopeter lens (Nikon, Melville, NY, USA) and a lid speculum (Alfonso Eye Speculum, Storz®, Bausch & Lomb Inc., San Dimas, CA, USA). Pupils were dilated with 0.5 tropicamide and 2.5 phenylephrine eye drops applied one hour before the examination. All exams were performed by the lead author, an ophthalmologist qualified to conduct ROP screening. All patients diagnosed with threshold ROP were treated with laser photoagulation. The ophthalmological examinations were initiated between the fourth and sixth weeks of life and were repeated weekly or biweekly, as per the Brazilian guidelines for ROP screening, until full vascularization of the retina reached zone 3 (the most peripheral temporal retinal zone), or until full remission of ROP after treatment.

The study protocol was approved by the HCPA Research Ethics Committee, under number 03-248.

**RESULTS**

Of all 407 patients screened for ROP, 232 (57.0%) were female and 252 (61.9%) were small for gestational age (SGA) (<10th percentile). Across the entire cohort, BW ranged from 505 g to 2 000 g, with a mean of 1 205.5 g (SD, 277.4), and GA ranged from 24 to 37 weeks, with a mean of 30.3 weeks (SD, 2.2) (Table 1). Table 2 shows the prevalence of all stages of ROP, estimated at a 95% CI, in the four patient groups (classified by BW). Some degree of ROP was identified in 104 patients, or 25.5% of cases, and severe ROP occurred in 24 (5.8%). The disease reached stage 1 in 11.3% of the patients (46), stage 2 in 8.4% (34), and [threshold] stage 3 in 5.4% (22). One patient developed ROP up to stage 4 (partial retinal detachment), despite two laser treatments, and required a scleral buckle to stop ROP progression, and one patient reached stage 5 (complete retinal detachment), after missing the scheduled laser treatment following NICU discharge, developing bilateral retrolental fibroplasia and subsequent blindness (resulting in 0.2% overall prevalence for ROP-induced vision deficit). The mean BW and GA for all patients with some level of ROP were 1 050.6 g (SD, 270.8)
and 29.1 weeks (SD, 2.3), respectively (data not shown), and the mean GA for all patients with threshold (laser-treated) ROP was within the 37th week of adjusted GA. Table 3 displays the characteristics of all laser-treated patients.

### DISCUSSION

The HCPA NICU has 20 intensive-care beds and is fully equipped for critical care, including pulse oximetry (for monitoring preterm infants under oxygen therapy and mechanical ventilation). During the study period, 407 VLBW premature infants survived from birth through the complete observation period (up to the 45th week of adjusted GA). The data suggest that 92.6% of all patients admitted to the HCPA NICU from the population deemed at risk for ROP were screened for the disease.

Programs to prevent ROP-induced blindness were initiated in many countries beginning in the 1980s, when the CRYO-ROP study demonstrated the first positive results from treatment of this disease with cryotherapy (13). Data from CRYO-ROP—a prospective, randomized, and multicenter study that reported ROP incidence based on a large number of patients and was conducted by well-trained, validated, and consistent examiners working under a rigorously designed protocol—were considered the most reliable statistics on ROP prevalence. The incidence of any stage of ROP in the CRYO-ROP study reached 65.80%. Stage 3 was the most active stage of the disease (observed in 17.8% of patients). Pre-threshold ROP was found in 17.8% of the overall cohort of 4 099 infants weighing less than 1 251 g at birth, whereas threshold ROP (defined above) was found in only 6.00% (15).

Although the initial results of the Early Treatment for Retinopathy of Prematurity Cooperative Group (ET-ROP) study, published in December 2003, showed significantly better ROP outcomes than the CRYO-ROP study, after nine months of pre-threshold treatment (16), the authors of the current study, who began prospective data collection in 2002, preferred to use the classical indication for treatment (i.e., threshold ROP). This treatment indication is still used by many ophthalmologists around the world, and both options (treatment at pre-threshold and threshold ROP) are suggested in the Brazilian ROP guidelines (10).

The study by Gilbert et al. in 2005 suggested that the infant population at risk for severe ROP in highly developed countries differs from that in less developed countries (5). However, it should be noted that 1) most published data on ROP come from selected NICU series, and 2) due to the intensive care setting, these types of series are rarely validated.
in terms of population and epidemiology, especially in Brazil and other Latin American countries.

In Brazil, Graziano et al. reported retinopathy of prematurity among infants with GA <37 weeks (i.e., outside the parameters for BW and GA stipulated in the Brazilian ROP screening guidelines) (20), as of 2000. A study in the northeastern city of Recife reported ROP in 51.89% of infants screened for the disease at a level-3 hospital in a metropolitan area of Delhi. This report called attention to the need for more ophthalmologists qualified to perform ROP screening in India. This same situation has been found in Brazil, where ROP screening programs are only available in major cities and are usually limited to university-level hospitals (14).

**Conclusion**

The overall ROP prevalence of 25.5% found in the current institutional study, and the percentage of infants diagnosed with severe disease (about 5.8% of infants with BW <1,500 g or GA <32 weeks—the population deemed at risk for ROP according to the Brazilian guidelines for ROP screening), were similar to the findings of other studies with a similar design. The authors of the current study believe the HCPA NICU is achieving better control by the nursery staff in their delivery of oxygen to infants under mechanical ventilation by distributing adequate information about the important role this therapy can play in decreasing the incidence of severe ROP among the neonates it delivers. As mentioned above, during the study period, only one patient developed ROP up to stage 4 (after two laser treatments) and one patient (0.2% of the overall cohort) progressed to stage 5 (blindness).

Although the incidence of ROP appears to be higher in North and Northeast Brazil (where ROP is still being described in infants with BW outside the recommended parameters of the Brazilian ROP screening guidelines) (20), as of the current study, which was based on institutional data, no nationwide survey has been conducted to confirm this trend. A comprehensive national study of ROP incidence is therefore recommended to verify possible regional differences in the prevalence of the disease.
RESUMEN

Prevalencia de retinopatía del prematuro: estudio transversal institucional de niños prematuros en Brasil

Objetivo. La retinopatía del prematuro (RP) es la principal causa de ceguera infantil en la mayoría de los países desarrollados. El objetivo de este estudio fue verificar la prevalencia de esta afección en todos los niños prematuros de muy bajo peso al nacer ingresados en un hospital docente de tercer nivel de Porto Alegre, Rio Grande do Sul, Brasil.

Métodos. Estudio transversal institucional de 407 niños prematuros que nacieron entre 2002 y 2007 con un peso de 1 500 g o menos, o 32 semanas de edad gestacional o menos. Todos los niños tamizados para RP se examinaron después de la cuarta semana de vida y tuvieron seguimiento hasta la semana 45 de edad gestacional ajustada. La prevalencia de RP se estimó con un intervalo de confianza de 95%.

Resultados. De los niños tamizados, 104 (25.5%) presentaron algún grado de RP en uno o ambos ojos, mientras 27 (5,58%) de ellos tuvieron tratamiento para evitar la pérdida de la visión, según los criterios del Estudio Multicéntrico de Crioterapia para la Retinopatía del Prematuro (CRYO-ROP), realizados en los Estados Unidos de América). Según los criterios de la Clasificación Internacional de la Retinopatía del Prematuro (ICROP), la enfermedad alcanzó los niños de 1, 2 y 3 en 46 (11,3%), 34 (8,4%) y 22 (5,4%) niños, respectivamente. Un niño desarrolló la enfermedad hasta el estadio 4 (desprendimiento parcial de la retina) y uno alcanzó el estadio 5 (desprendimiento completo de la retina), lo que representó una prevalencia de ceguera por RP de 0,2%.

Conclusiones. La prevalencia de RP en este estudio institucional (25.5%) es similar a los resultados obtenidos en países desarrollados. Se recomienda realizar una encuesta exhaustiva nacional sobre RP en Brasil para determinar si existe alguna diferenciación regional en la prevalencia de esta enfermedad.

Palabras clave
Ceguera, prevención y control; retinopatía de la prematuridad, epidemiología; prevalencia; Brasil.

REFERENCES