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Risk factors associated with retinopathy of prematurity and visual alterations in infants with extremely low birth weight

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ABSTRACT

Objective. Retinopathy of prematurity (RoP) is a retinal vascular disease and a frequent cause of blindness in infants. Our objective was to measure the frequency of RoP in infants with extremely low birth weight (ELBW, < 1,000 g) at the National Institute of Perinatology, Neonatal Intensive Care Unit (NICU), weighing the association of RoP with several risk factors and their results, such as refractive errors and strabismus. **Material and methods.** We carried out two cross-sectional observations of our prospective study: one near birth, and the second, after a long-term follow-up. Funduscopic examination was performed while the infants were in the NICU to detect RoP. Infants with RoP were followed up by means of visual examinations during an average 8-year period and results were compared with those of infants with ELBW without RoP. **Results.** Of the 139 screened infants at the NICU, 24.4% were identified with RoP: 79% of these with grade I retinopathy; 18% with grade II, and one infant with grade III retinopathy. The zones involved were as follows: zone 1, 12%; zone 2, 79%, and zone 3, 9%. The following were associated with retinopathy: eclampsia (p = 0.003); gestational age (0.01); multiple gestation (0.03); days of stay at NICU (< 0.001); mechanical ventilation (0.001); hypoxia (0.01); oxygen therapy (< 0.001); apnea (0.005); acidosis (0.001), and hypercapnia (0.001). Retinopathy was self-limited in all children. We found no differences in frequency of refractive errors and strabismus between children with RoP and controls. **Conclusions.** We observed a moderately high frequency of RoP in infants with ELBW in Mexico City and recommended early mandatory screening for early intervention.

Factores de riesgo asociados con retinopatía de la prematurez y alteraciones visuales en infantes nacidos con peso extremadamente bajo

RESUMEN

Objetivo. *La retinopatía de la prematurez (ReP) es una enfermedad vascular de la retina y una causa frecuente de ceguera en infantes.* ***Objetivo.*** *Medir la frecuencia de la ReP en neonatos con peso extremadamente bajo al nacimiento (PEBN < 1,000 g) provenientes de una Unidad de Cuidados Intensivos Neonatales; se midió la asociación de ReP con varios factores de riesgo y sus resultados como errores refractivos y estrabismo.* ***Material y métodos.*** *Se llevaron a cabo dos cortes temporales a partir del estudio prospectivo: uno en el periodo neonatal y el segundo tras un seguimiento a largo plazo. Se realizó un examen fundoscópico en cada niño en la Unidad de Cuidados Intensivos para detectar ReP. Los niños ingresaron a un programa de seguimiento de la función visual durante un promedio de ocho años, sus resultados fueron comparados con los de niños con PEBN sin ReP.* ***Resultados.*** *De 139 niños examinados en la UCIN, 24.4% fueron identificados con ReP: 79% retinopatía grado I; 18% grado II y un niño con grado III. Las zonas comprometidas fueron: zona 1, 12%; zona 2, 79% y zona 3, 9%. Los factores de riesgo asociados fueron: eclampsia (p = 0.003), edad gestacional (0.01), gestación múltiple (0.03), días de estancia hospitalaria (< 0.001) y baja ventilación mecánica (0.001); hipoxia (0.01); terapia con O2 (< 0.001); apnea (0.005); acidosis (0.001) e hipercapnea (0.001). Al final del seguimiento la ReP se autolimitó en todos los niños. No hubo diferencias en la frecuencia de errores refractivos y estrabismo entre niños con ReP y controles.* ***Conclusiones.*** *Se encontró una frecuencia moderadamente alta de ReP en niños con peso extremadamente bajo al nacer, en la Ciudad de México, y se*

recomienda el examen temprano obligatorio de ReP para iniciar un tratamiento temprano.

Palabras clave. *Peso extremadamente bajo al nacer. Peso bajo al nacer. Prematurez. Retinopatía de la prematurez. Errores refractivos. Miopía. Estrabismo.*

Key words. Extremely low birth weight. Low birth weight. Preterm birth. Retinopathy of prematurity. Refractive errors. Myopia. Strabismus.

INTRODUCTION

Vision is one of the most important senses necessary to develop in human infants higher cerebral functions such as perception, cognition, fine motor skills, and others. Premature newborns have a higher risk for developing neuromotor, sensory, behavioral, cognitive, and other brain function sequelae. The literature underscores that retinopathy of prematurity (RoP), refractive errors, and strabismus comprise the main visual complications of premature newborns. RoP is characterized by abnormal retinal-vessel proliferation due to two basic conditions in premature newborns:[1]

- A visual system exposed to an aggressive environment, and
- The direct or indirect effects of diseases on the immature visual system.[2,3]

RoP is believed to be due to multifactorial causes and is the main disease that produces blindness in infancy and childhood.[4,5] Frequency of RoP is higher in infants with a lower birth weight and has been reported as follows:[6]

- 500-1,000 g, 48.2%.
- 1,001-1,500 g, 18.7%, and
- 1,501-2,000 g, 10%.

In many countries, the incidence of RoP is unknown because variability in incidence is related with differences in quality of clinical assistance, oxygen support, among other factors.[7] Thus, each specialized center must know their own statistics and RoP-related risk factors because there are differences from center to center, city to city, and country to country. In the specialized literature, RoP has been associated with several risk factors, among which the following are the major ones: low birth weight; short gestational age; days of oxygen treatment and duration of mechanical ventilation; other risk factors significantly associated with RoP include days of stay in the Neonatal Intensive Care Unit (NICU), use of surfactant, intraventricular hemorrhage, sepsis, candidemia, and others.[8]

We report the results from our observations on two points-of-analysis of our prospective follow-up study on infants born with extremely low birth weight (ELBW). The first is early analysis at one of the principal NICU in Mexico City, at which infants with ELBW were screened for RoP while they were in-patients, and the second, later during long-term follow-up when refractive errors and strabismus can be found in these infants. Possible relationships with several perinatal risk factors were analyzed. Our objectives included the following: measurement of RoP frequency in infants with ELBW at the NICU; measurement of the association of RoP with several risk factors and their results at follow-up.

MATERIAL AND METHODS

Subjects

We selected infants born between January 2000 and June 2008 with birth weights of ≤ 1,000 g who were screened for RoP at the NICU. We formed two groups for analysis: the first, infants with identified RoP (the RoP group), and the second, infants without RoP (the control group). All of these infants were recruited from the Prospective Study of Follow-up of High-risk Infants for Neuropsychologic Alterations of the Mexico City-based National Institute of Perinatology (INPer). We studied 447 newborns with ELBW. Of this population, 139 (31%) were screened for RoP and completed their visual and ophthalmologic follow-up of 8 years on average. Finally, 34 newborns were identified as having RoP. Inclusion criteria for the follow-up program have been described elsewhere.[9,10] Exclusion criteria comprised the following: congenital anomalies involving the visual pathway; Norrie disease; persistence of primary vitreous; microphthalmia (of syndromic or non-syndromic transmission), and maternal-fetal infections in the first trimester of pregnancy (toxoplasmosis, rubella, cytomegalovirus, herpes virus, syphilis, and the human immunodeficiency virus).

We obtained the following maternal information from hospital charts: history of high blood pressure; diabetes mellitus; hypothyroidism; infections, and other severe maternal diseases. From infant charts,

we obtained information on the following: conceptional age at birth (calculated from day 1 of the last menstrual period or ultrasound [US] measurement and confirmed by neonatal examination); single or multiple pregnancies; weight at birth; Apgar scores at 1 and 5 min; gender; days of stay at the NICU; days of mechanical ventilation; days of oxygen exposure; administration of prenatal steroids, and exogenous surfactant.

Moreover, we searched for specific RoP risk factors such as acidosis (pH < 7.25), hyperoxemia (PaO_2 > 80 mmHg), hypoxemia (PaO_2 < 50 mm Hg), hypercapnia ($PaCO_2$ > 50 mmHg), hypocapnia ($PaCO_2$ < 35 mmHg), blood transfusions, apnea, necrotizing enterocolitis, persistence of ductus arteriosus, sepsis, intraventricular hemorrhage, and exposure to the drugs dopamine, dexamethasone, and indomethacin. Intraventricular hemorrhage was determined by cranial ultrasonography while the infants were hospitalized in the NICU and was classified after Pappile, *et al.*[11] Parents of infants were informed concerning the purposes and benefits of the research and the importance of their infants' participation. Informed and signed consent was required according to the Institute's Research Committee and the Declaration of Helsinki.

Procedures

Funduscopic examination was conducted under pharmacologic dilatation of the pupil while infants were at the NICU. We used tropicamide 10%, phenylephrine 2.5%, and proparacaine 0.5% eye drops 30 min prior to eye examination. We utilized an indirect bi-ocular ophthalmoscope, a pediatric blepharostate, scleral depressor, and a 28-diopter magnifier lens. At the end of the study, we administered prophylactic antibiotic cream locally. All examinations were performed by the same Ophthalmologist (MS-V) under monitoring of vital signs with a test-retest score of 99%; the examinations have been validated with high sensitivity (> 86%) and specificity (> 92%) for application in premature infant populations.[12]

The degree of RoP was staged according to the international classification as follows:[13] RoP I, line of demarcation of an avascular region with clear non protruding edges; RoP II, line of demarcation protruding from the avascular region; RoP III, extra-retinal, fibro-vascular proliferation with terminal vessels in a fan-like arrangement and hemorrhage in cord; RoP IV, tractional peripheral retinal detachment: RoP IVa, retinal detachment not including macular or foveal regions; RoP IVb, retinal detachment including macular or foveal regions, and RoP V, total retinal detachment.

Retinal zones involved in RoP were classified as follows:

- **Zone 1.** In the posterior pole centered in the papilla with a circle in which its radius is twice the distance between papilla maculae.
- **Zone 2.** Or peripheral retina centered in the papilla and extending to a circle zone between interior circle of region I and external circumference reaching the nasal *Ora serrata*, and
- **Zone 3.** Or extreme periphery, residual zone in crescent-moon between region II external circle and temporal *Ora serrata*.

Follow-up examinations were conducted until RoP resolution or retinal maturation was achieved. Treatment criteria for RoP were performed according to evolution of disease severity by stage, location by zone, and extent of clock distribution. Treatment was effected with transpupillary diode laser photocoagulation.[14]

Infants were prospectively followed-up by serial visual and ophthalmologic examinations at 6-month intervals by means of the following methods: refractive errors were measured employing a variety of techniques depending on the capabilities of the child and included static retinoscopy, cycloplegic retinoscopy, phoropter examination, and subjective refraction. We also utilized the Snellen E chart for children aged 3 years and over because children at this age were able to indicate the direction of the legs of the letter E by pointing with a finger or could write the direction. We tested visual acuity in each eye separately and bi-ocularly. We employed the pupil reflex measurement of ocular parallelism and the eye movement examination with the aid of a specialized box to test for refractive errors.

For diagnosis of strabismus, we utilized the Hirschberg corneal reflex test. This test consisted of observation of the position of the corneal reflex when a light is directed into the child's face. Light emission must be centered on the right and left pupils. Deviations in nasal, temporal, or in downward or upward direction of the eyeball suggest strabismus. The test has been validated with high sensitivity (90%) and specificity (99%) scores.[15] All examinations were performed by the same Ophthalmologist with a test-retest score of 99%.

Statistical analysis

Sample size was calculated after the Orozco-Gómez, *et al*.[16] study with 80% study power to detect the presence of variables-of-interest. We calculated frequencies and percentages of binomial variables, medians for discrete variables or when continuous variables were non-normally distributed, and average ± standard deviation (SD) for continuous variables and with normal distribution. Group comparison for qualitative data was performed by the χ^2 test; when cell numbers were < 5, we used the Fisher exact test. We employed the Student t test for quantitative variables, and performed relative risk (RR) calculation for each risk factor for RoP. We utilized Statistical Package for Social Sciences (SPSS) 17.0 software for statistical calculations.

RESULTS

Of 139 screened infants at our NICU, 34 newborns (24.4%) were identified as having RoP to some degree and 105 (75.6%) did not have RoP. Maternal median age at time of birth was 28 years for both groups. Comparison of maternal morbidity demonstrated significant differences between Control and RoP groups in frequency of eclampsia (Table 1).

Comparison of several non-optimal-at-birth infant variables demonstrated significant differences with disadvantaged values for the RoP group in mean gestational age at birth, multiple gestation frequency, days of stay at the NICU, days under mechanical ventilation, days under oxygen therapy, and Apgar scores (Table 2). Comparisons of risk factors for RoP between groups showed significant differences in frequency of apnea, acidosis, and hypercapnia (Table 3).

Table 1. Maternal risk factors in RoP and control groups. Relative risk calculations.

	RoP group (n = 34)	Control group (n = 105)		
Variable	Yes	Yes	RR (95% CI)	P
Preeclampsia	7 (20%)	33 (31%)	0.64 (0.3-1.3)	0.22
Eclampsia	5 (15%)	2 (2%)	3.25 (1.8-5.7)	0.003
Chorioamnionitis	3 (9%)	10 (9%)	0.93 (0.3-2.6)	0.90
Diabetes	2 (6%)	5 (5%)	1.17 (0.3-3.9)	0.79
HELLP syndrome	1 (3%)	1 (1%)	2.07 (0.5-8.5)	0.39

RoP: retinopathy of prematurity. RR: relative risk. 95% CI: 95% confidence interval. HELLP syndrome: hemolytic anemia-elevated liver enzymes-low platelet count syndrome.

Table 2. Comparison of the clinical characteristics of children with and without retinopathy of prematurity (RoP).

Variable	RoP group (n = 34)			Control group (n = 105)			
	n	Median	Minimum-Maximum	n	Median	Minimum-Maximum	p
Age at birth (weeks)	34	228	25-31	105		25–33	0.01*
Weight at birth (g)	34	7720	410–1,000	105	820	530 –1,000	0.1*
Stay at NICU (days)	34	553.5	1-94	105	37	1-89	< 0.001*
Mechanical ventilation (days)	33	112	0-47	91	3	0-66	< 0.001*
Exposure to O_2 (days)	34	880	31-117	105	60	1-179	< 0.001*
1-min Apgar score	34	4.5	1-8	105	7	1-8	0.002*
5-min Apgar score	34	8	4-9	105	9	5-9	0.03*
Masculine gender	13	-	-	42	-	-	
Feminine gender	21	-	-	63	-	-	0.8**
Single gestation	22	-	-	86	-	-	
Multiple gestation	12	-	-	19	-	-	0.03**

NICU: neonatal intensive care unit. n = number of cases. *Mann-Whitney U test. **χ^2 test.

Table 3. Relative risk calculations and risk factors for RoP.

Variable	RoP group (n = 34) Yes	Control group (n = 105) Yes	RR 95% CI	P
Apnea	33 (97%)	79 (75%)	7.95 (1.1-55.6)	0.005
Enterocolitis	22 (65%)	47 (45%)	1.86 (1.0-3.4)	0.04
Persistence ductus arteriosus	19 (56%)	34 (32%)	2.05 (1.4-3.6)	0.01
Dopamine	6 (18%)	4 (4%)	2.76 (1.5-5.0)	0.007
Acidosis	26 (76%)	46 (44%)	3.02 (1.4-6.2)	0.001
Hypoxemia	27 (79%)	59 (56%)	2.37 (1.1-5.0)	0.01
Hypercapnia	26 (76%)	47 (45%)	2.93 (1.4-6.0)	0.001

RoP: retinopathy of prematurity. RR: relative risk. 95% CI: 95% confidence interval.

Table 4. Ophthalmologic features found in the follow-up of children with and without retinopathy of prematurity (RoP).

Variable	RoP group (n = 34) Yes	Control group (n = 105) Yes	P
Strabismus	2 (6%)	4 (4%)	0.6*
Myopia	2 (6%)	4 (4%)	0.6*
Astigmatism	15 (44%)	33 (31%)	0.1**

*Fisher exact test. **χ^2 test.

Of the group of infants with RoP, 27 (79%) developed RoP I, six developed RoP II (18%), and one infant developed RoP III (3%); no infant developed RoP IV or V. The following regions were involved: zone 1 was compromised in four infants (12 %); zone 2, in 27 (79%), and zone 3, in three (9%) infants.

Median age at the first ophthalmologic examination was not different between the control and RoP groups, and median age was 6 weeks after birth for both groups. Median age at the last follow up-period examination was 4 years for both groups. Four infants required treatment with transpupillary diode laser photocoagulation and treatment outcome was considered favorable with regression of RoP. Throughout the 8 years of vision and ophthalmologic monitoring follow-up, we observed that RoP was self-limited in 100% of children. No blindness was found in this sample. We found no significant differences in strabismus frequency and refractive errors between the control and RoP groups (Table 4).

DISCUSSION

Main findings

Although RoP frequency and associated risk factors have been extensively studied worldwide, its causes may change by NICU, city, or country, and each site must investigate its own statistics. In our study, we weighed the frequency of RoP in an 8-year follow-up period in infants with ELBW at our NICU at the INPer in Mexico City and found an overall RoP frequency of 24.4%. Of this group, 79% developed RoP I, 18%, RoP II, and one infant developed RoP III. No infant developed RoP IV or -V. Involved zones included the following:

- Zone 1 (12%).
- Zone 2 (79%), and
- Zone 3 (9%).

RoP-associated risk factors in our sample comprised eclampsia, lower gestational age at birth, multiple gestation, days of stay at the NICU, days under mechanical ventilation and days under oxygen therapy, 1- and 5-min Apgar scores, apnea, acidosis, and hypercapnia. At 8 years of follow-up, we observed that RoP was self-limited in 100% of the infants and found no children with blindness in our sample.

Comparison with other studies

Although the prevalence of RoP in Mexico is unknown,[17] prior studies for identification of RoP have been conducted in the country. For example, Orozco-Gómez, *et al.*[16] carried out a prospective study to determine the prevalence of RoP between 1991 and

2004 in 170 preterm infants weighing < 1,500 g at birth and born at < 35 weeks of pregnancy. Screening was conducted by means of indirect ophthalmoscopy. There were 46 infants in RoP stages I-III, with a prevalence of 10.61%; 12% of these infants were at threshold stage, with a prevalence of 2.72/100. Flores-Santos, *et al.*,[6] conducted another prospective study to determine RoP frequency at a public-university medical hospital in preterm infants. Screening was performed by means of indirect ophthalmoscopy. The authors found a RoP prevalence of 22.2% in premature infants; 11.42% had threshold retinopathy and underwent cryotherapy. In the 500-1,000-g weight-at-birth group, 48.2% had RoP in any stage and 27.5% had threshold retinopathy. In the 1,001-1,500-g group, 18.7% had any stage of RoP and 8.8% had stage III. In the 1,501-2,000-g group, 10% had any stage RoP and 5.2% underwent cryotherapy. Eighty six percent of infants with threshold retinopathy received cryotherapy and experienced complete recovery, but 5% developed unilateral, and 9% bilateral, retinal detachment. There are several differences between these studies and our results. The Orozco-Gómez, *et al.*, study showed a lower frequency of RoP, but the authors did not study infants separately by age in their group of premature infants and included premature newborns with higher age and weight at birth. The Flores-Santos, *et al.,* study found a higher frequency of RoP in the 500-1,000-g weight-at-birth group; this difference can be explained by certain features of our premature infants who had a lower RoP frequency.

One of the most influential prospective studies to ascertain the natural history of RoP was the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study. Investigators followed a large cohort of infants with RoP between January 1986 and November 1987.[18] Frequency of RoP in infants with a birth weight of < 1,251 g was 66%. Data from this research showed that cryotherapy results in favorable outcomes. However, many children had visual impairment as a significant sequelae. Researchers reported a high frequency of refractive errors, strabismus, and cortical blindness in children with the antecedent of preterm birth in the follow-up. This result is not in line with our findings; contrariwise, our data is in agreement with the favorable results obtained from the Chow, *et al.* study.[19] We think that the differences can be explained by the time gap between both studies, better quality of care of our infants with ELBW, and by introduction of novel technologies that were utilized in NICU care for preterm infants.

RoP origin and evolution

Several hypotheses have been postulated to explain the increased frequency of RoP development in premature infants worldwide, such as increased levels of cytokines,[20] candidemia sepsis,[21] blood transfusion,[22] and others. Prevention has been studied for the early-treatment effects of several actions, such as Dexamethasone administration,[23] reduction of light,[24] erythropoietin administration,[25] and others.

In many NICUs throughout the world, statistics on RoP frequency are unknown or inexact. When RoP is measured, the calculation numerator must be the number of infants with RoP, while the calculation denominator must be the number of infants screened, as performed in our study. Our data showed a relatively higher RoP frequency and suggest the recommendation of universal screening of all newborns at high risk for RoP when comparing the results with those of specialized reference hospitals.[26]

On the other hand, in several regions where data are collected of known prevalence of blindness and other visual defects in school children, RoP is the main cause of vision impairment.[27] Moreover, RoP presentation generally does not occur alone; impairment is frequently associated with severe neuromotor retardation and other cognitive sequelae. The magnitude of this problem is increasing in underdeveloped countries[6,27-29] in which survival of ELBW infants is increasing each year. Under these conditions, there is growth of a higher prevalence of severe RoP and blindness and of its disease burden in these societies.

In the present work, in an NICU with premature newborns with ELBW mortality reaching a frequency of 38.7%[30] (a number considered as a high infant-mortality index), RoP frequency is relatively low, which may be a reflection of good infant care and early initiation of measurement interventions implemented by the NICU staff.

Although intraventricular hemorrhage is highly related with lower visual acuity, strabismus, and nystagmus,[31] these visual disabilities can be associated not only with RoP, but also can result from periventricular leukomalacia, or a white- or gray-matter lesion in the visual thalamo-cortical pathway or in the visual areas of the cortex. We did not observe differences between control and RoP groups in frequency of strabismus and refractive errors. This absence of differences may be related with the quality of infant care in the NICU.

Exogenous surfactant administration for respiratory distress began in the 1990s in several NICU, extended rapidly, and was associated with an observed improvement of body oxygen levels. Oxygen monitors were also introduced in the same decade. Blood oxygen levels have been related with RoP because some researchers hypothesized that these higher levels of oxygen administration inhibited blood vessel development. However, oxygen is not the only factor responsible for RoP development. Carbon dioxide fluctuations (hypoxia, hyperoxia, and hypercapnia) have also been suggested to result in two well-defined phases of retinal damage.[32]

Nearly 10% of infants with an antecedent of RoP require eyeglasses when they grow up and may need to change their prescriptions each year until the age of 7 years. At this latter age, children must be reevaluated by the Ophthalmologist according to neurodevelopmental follow-up protocols and must be studied by visual field test, intra-ocular pressure measurements, ocular movement examination, visual acuity tests, measurement for the eyeglasses required, and correction in the case of using the latter.[33,34] Our observation failed to demonstrate significant differences between the control and RoP groups with respect to refractive errors and strabismus. Additional studies are required to ascertain the response to this question.

A high prevalence of myopia has been reported in infants with an antecedent of preterm birth, and other refractive errors such as astigmatism and anisometropia have also been reported as occurring more frequently in preterm-born infants when compared with infants born at term.[35] Myopia in premature infants is a special case with rapid progression that can reach amblyopia. Prevalence of strabismus in infants with an antecedent of preterm birth is 57% at 5 years of age in infants born prior to 28 weeks of gestation.[35] The high prevalence of strabismus may be related with refractive errors, severe RoP, and with the infant's general health state.

CONCLUSION AND RECOMMENDATIONS

In summary, we found a moderately high frequency of RoP in infants with ELBW related with several maternal and neonatal risk factors at one of the main NICU in Mexico City. These results suggest that early identification and treatment must be performed to avoid long-term sequelae. Based on these results, we recommend mandatory RoP screening in high-risk infants. We also recommend that premature high-risk infants with antecedents of RoP and visual impairment must be included in early visual intervention programs to promote their integration into familial, academic, and social environments.

DISCLOSURES

The authors declare that this study was not industry-supported research.

The authors declare that there is no conflict of interest.

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