Frequency and severity of retinopathy of prematurity in a neonatal intensive care unit

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Abstract

Introduction: Retinopathy of prematurity (ROP) is a disease where retinal blood vessels do not develop normally and may cause visual damage and blindness. **Objective:** To determine the frequency and severity of ROP in preterm newborns. **Method:** A descriptive, comparative study was carried out within the 2009-2013 period. Patients' general characteristics were recorded, including gestational age and postmenstrual age at the moment of ophthalmologic examination, as well as ROP severity and type of treatment. **Results:** A total of 326 preterm newborns were included: 47.8 % ($n = 156$) had ROP; in 21.1 % it was severe (stage ≥ 3). Median gestational age was 28 weeks in preterm newborns with ROP, median birth weight was 1000 g, and median postmenstrual age at ophthalmological examination was 36 weeks. Of the infants with ROP, 71.1 % received treatment: 63.4 % of those who had mild ROP and 100 % of those with severe ROP. **Conclusions:** ROP frequency was high, higher than that reported in developed countries and similar to that in developing countries. The frequency of severe ROP was also higher. It is necessary for effective programs for the detection and opportune treatment of ROP to be established.

KEY WORDS: Retinopathy of prematurity. Preterm neonate. Photocoagulation.

Introduction

Retinopathy of prematurity (ROP) is a fibro- and vasoproliferative peripheral vitreoretinopathy that occurs in premature newborns (NB) undergoing oxygen therapy, the etiopathogenesis of which is still unknown.¹ It was described by Terry² in 1942 as retrolental fibroplasia. In 1951, Heath named it retinopathy of prematurity.³ ROP is the most common cause of childhood blindness in developed and developing countries.^{1,4} Advances in neonatal intensive care have increased extremely low birth weight (ELBW) premature infants survival and, therefore, the number of children at risk for developing severe ROP has also increased.⁵

In the 1950's, Kinsey⁶ reported the first ROP epidemic and associated it with oxygen therapy, which led to restrict its use. In the decade of the 80's, a second

epidemic occurred;⁷ currently, the third one is considered to be occurring.

The incidence of ROP and its serious modality has shown different trends. In 1956, the CRYO-ROP⁸ group reported an incidence of 27 %, while in a 1986 and 1987 multi-center study, an increase of 65.8 % was reported in premature NBs with < 1251 g weight and 81.6 % in premature infants with body weight < 1000 g.⁹ However, between 1995 and 1996, an incidence decrease to 41.3 % was reported in this same group.¹⁰

The ETROP group, between 2000 and 2002, reported an incidence of 68 %, similar to that reported by the CRYO-ROP group in 1986 and 1987.^{9,11}

The ROP incidence reported in developed countries is highly variable: it ranges from 9.3 to 68 %.¹²⁻¹⁷

There are only few reports on the incidence of ROP in Mexico. In the studies that have been carried out in different centers it ranges from 13.3 to 30 %.¹⁸⁻²¹

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Screening for ROP early detection is considered to be a priority since 1988.⁵ The main purpose of screening is to identify all premature infants that require treatment for ROP or tighter ophthalmological follow-up, as specified in the latest recommendations established by the American Academy of Pediatrics, the American Association of Pediatric Ophthalmology and Strabismus and the American Academy of Ophthalmology.²²

The recommendations for screening are the following: birth weight $\leq$ 1500 g or gestational age $\leq$ 32 weeks; it should be carried out by an ophthalmologist with experience in the evaluation of premature children, between weeks 4 and 6 of chronological age, or between weeks 31 and 33 of postconceptional age; successive evaluations will be determined based on the findings of the first ophthalmologic examination.²²

A significant number of children who develop severe ROP will have visual (14.5 %) and structural (9.1 %) unfavorable results in spite of ablative treatment with laser or cryotherapy.^{23,24}

The purpose of the present study was to identify the frequency and severity of ROP, as well as the administered treatment in premature NBs who were admitted to the neonatal intensive care unit (NICU) or who were provided care to at the outpatient ophthalmology clinic of a tertiary care hospital.

Method

Descriptive, comparative study of patients admitted to the NICU and to the Ophthalmology Outpatient Clinic of the Pediatrics Hospital of Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, where patients referred from other hospital units of the southern area of Mexico City, some states of the Mexican Republic and private hospitals are cared for. The protocol was approved by the Local Research and Ethics Committee of the hospital where the research was conducted.

Premature NBs with gestational age $\leq$ 32 weeks at birth or birth weight $\leq$ 1500 g, chronological age $\geq$ 4 weeks, who received supplementary oxygen and who were admitted to the NICU or were looked after at the ophthalmology outpatient clinic within the 2009-2013 period were included.

The following data were recorded: gestational age, birth weight, gender, Apgar score at 1 and 5 minutes, type of delivery, comorbidity, use of prenatal steroids, exogenous surfactant and supplementary oxygen, chronological age and postconceptional age at the time of ophthalmologic evaluation, ROP classification and severity and administered treatment.

ROP international classification was used,²⁵ which groups it into 5 stages and 3 zones. In addition, whether there was plus disease (venous dilation, arteriolar tortuosity and posterior pole hemorrhages) was recorded. Severity was stratified in 2 categories: Mild ROP, comprising stages 1 and 2, and serious ROP, which comprises stages 3, 4 and 5.²⁶

NBs who met the inclusion criteria were examined and treated by ophthalmologists of the hospital unit. Two investigators collected first assessment and follow-up data from the medical records.

Statistical analysis

Descriptive statistics was used; for qualitative variables, simple frequencies and percentages were calculated, and for quantitative variables, medians and intervals, since most variables did not follow a normal-like distribution.

For comparative analysis, two groups were formed: children with and without ROP. For the comparison of some variables, the chi-square test or Fisher's exact test were used for qualitative variables, and Mann-Whitney's U-test for the quantitative ones.

For the database generation and statistical analysis, the statistical program SPSS, version 17, was used.

Results

Three hundred and twenty-six NBs were included between January 2009 and December 2013: 156 children with ROP and 170 without ROP. Table 1 shows the general characteristics of the NBs of each group; both gestational age and birth weight were lower in children with ROP. Oxygen usage time was longer in the children with ROP ($p = 0.0001$). Surfactant was used more often in NBs who developed ROP ($p = 0.001$). There was no difference between groups in postconceptional age at the moment of ophthalmologic examination, gender, type of delivery or prenatal steroid administration.

Table 2 describes the chronological age and postconceptional age at which the NBs were evaluated for the first time. The international recommendation on the ideal moment to perform the first ophthalmological examination is also shown.

Seventy-three percent of children who did not develop ROP had their first ophthalmologic evaluation performed between weeks 4 and 6 of chronological age. Of total patients with ROP, 40.4 % were examined between weeks 4 and 6 of chronological age, and only

Table 1. Characteristics of newborns with retinopathy of prematurity

Variable	With ROP (n = 156)		No ROP (n = 170)		p*
	Median (interval)		Median (interval)		
Gestational age	28 (24-34)		30 (23-35)		< 0.0001
Birth weight (g)	1000 (465-2290)		1260 (370-1775)		< 0.0001
1-minute Apgar	6 (0-8)		6 (2-9)		ns
5-minute Apgar	7 (2-9)		8 (2-9)		ns
Age at admission (days)	47 (1-154)		35 (1-150)		< 0.0001
Chronological age at ophthalmologic examination (weeks)	8 (2-22)		6 (3-21)		< 0.001
PCA [‡] at examination (weeks)	36 (30-52)		36 (30-51)		ns
Time of O ₂ use (days)	48 (2-135)		35 (3-98)		< 0.0001
	n	%	n	%	
Gender					
Male	80	76	97	57.1	ns**
Female	51.3	48.7	73	42.9	
Type of delivery					
Vaginal	29	18.6	36	21.2	ns**
Cesarean section	127	81.4	134	78.8	
Prenatal steroid	102	65.4	110	64.7	ns**
Surfactant	147	94.2	139	81.8	0.001**

*Mann-Whitney U-test.

**Mantel-Haenszel Chi-square test.

[‡]PCE = postconceptional age, ROP = retinopathy of prematurity, ns = not significant.**Table 2. Relationship between gestational age at birth and age at ophthalmologic examination**

Gestational age at birth, weeks	American Academy of Pediatrics recommendations ²²		HP CMN SXXI	
	Age at first examination (weeks)*		Age at first examination (weeks)*	
	Postconceptional	Chronological	Postconceptional	Chronological
22 [‡] (0)	31	9	—	—
23 [‡] (1)	31	8	28	5
24 (1)	31	7	36	12
25 (4)	31	6	31-41	6-16
26 (22)	31	5	30-43	4-17
27 (41)	31	4	31-44	4-17
28 (62)	32	4	32-45	4-17
29 (38)	33	4	33-44	4-13
30 (70)	34	4	34-52	4-22
31 [†] (11)	35	4	34-39	3-8
32 [†] (50)	36	4	36-42	4-10
33 (12)	—	—	37-42	4-9
34 (11)	—	—	38-41	4-7
35 (3)	—	—	39-40	4-5

*Recommendation in the United States.

**Hospital where the study was carried out.

[‡]This recommendation should be considered tentative rather than evidence-based, owing to the small number of survivors at this age.[†]If necessary.

Table 3. Retinopathy of prematurity frequency according to the international classification

Stage	Zone						Total	
	I		II		III		n	%
	n	%	n	%	n	%		
1	2	1.3	15	9.6	63	40.4	80	51.3
2	1	0.6	20	12.8	22	14.1	43	27.6
3	2	1.3	16	10.3	15	9.6	33	21.1
Total	5	3.2	51	32.7	100	64.1	156	100
Plus disease								
Stage I	0	0	4	2.5	1	0.6	5	3.2
Stage II	0	0	7	4.5	8	5.1	15	9.6
Stage III	2	1.3	13	8.3	8	5.1	23	14.7
Total	2	1.3	24	5.3	17	10.8	43	27.5

Eleven patients developed retinopathy of prematurity in a single eye.

4.4 % of children with severe ROP were assessed at that age.

Most NBs had more than one associated disease. Bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage and seizures were more common in the children with

ROP ($p < 0.05$). ROP frequency was 47.8 % ($n = 156/326$). In 145 patients, ROP was detected in both eyes and in 11 it was unilateral.

With regard to severity, 79.9 % had mild ROP, in 21.1 % it was severe and 27.5 % had disease plus. Stage of the disease and affected area are described in table 3; most patients had ROP at stages 1 and 2 and in zones II and III; none had stage 4 or 5 ROP.

Figure 1 shows the relationship between gestational age and ROP frequency and severity. The highest frequency (27.6 %) occurred in NBs with gestational age between 27 and 29 weeks; in this age group, the frequency of severe ROP was also higher (63.6 %).

As regards birth weight, ROP was more common in those who weighed between 751 and 1000 g (19 %); in that weight category, the proportion of severe ROP was also higher (60.6 %) (Fig. 2).

Patients who developed ROP had longer duration of oxygen supply; however, oxygen saturations that were used in these patients could not be determined because they all had been referred from other hospital units (Fig. 3).

Among the NBs with ROP, 71.1 % (111/156) received treatment: 63.4 % of those with mild ROP and 100 % of NBs with severe ROP. In 43.9 % (54/123) of the children with mild ROP, only paraocular dexamethasone was administered (100 µg/kg/dose), in 19.5 % (24/123), cryotherapy, laser photocoagulation or a combination thereof, in addition, paraocular steroid was used in 21

of these NBs. In 36.4 % (12/33) of NBs with severe ROP, steroid and cryotherapy were administered; in 27.3 % (9/33), cryotherapy, in 27.3 % (9/33), laser and paraocular steroid, and in 9 % (3/33), only laser.

Of total included patients, 67 (20.5 %) underwent a second evaluation. The interval between both evaluations had a median of 16 days (range of 5 to 69 days). Of these children, 23 (34.3 %) had ROP progression, 25 (37.3 %) had regression and 19 (28.4%) were found with no changes. Of the 15 patients who in the initial evaluation had retinal immaturity, 9 had progressed to ROP, 3 improved and 3 remained equal, i.e., with immaturity, in the second evaluation.

Discussion

ROP is an alteration in the development of the retina in premature NBs with low birth-weight that potentially causes blindness in a low but significant percentage. In full-term children, the retina is fully developed, so ROP does not occur in them; however, in premature NBs, retinal development is incomplete, and the degree of retinal immaturity depends mainly on the NB degree of prematurity.²²

The frequency of ROP in this study was high in comparison with that reported in some developed countries^{12,14,16} (although the VOND neonatal network reported 57 %),¹³ although it is within the range reported in Latin American countries, which ranges from 6.6 to 82 %;²⁷ it was also similar to that of countries with scarce development such as Saudi Arabia, where 56 % is reported.²⁸ In Mexico, ROP frequency records are scarce, in addition to inclusion criteria being diverse.¹⁸⁻²¹

The risk for developing ROP is not only determined by prematurity and low birth weight, but by other factors such as patient severity status during his/her stay in the NICU, comorbidity and the procedures they undergo there, i.e., patients managed at each hospital unit are different, which makes it difficult to compare the incidence rates between different institutions and even more so between different countries, especially developed ones, where there are well-established ROP detection policies.^{18,20,21}

The frequency of severe ROP was 21.1 %, which is also higher than that reported.²⁹ In Spain, an incidence of 15.6 %¹⁷ was recorded, while in the Netherlands it was 1.2 %.¹¹ In this study, it was similar to that recorded in Latin American countries, the figures of which range from 1.2 to 23.8 %.²⁷

The factors that increase the risk for developing ROP undoubtedly include gestational age and birth weight. In the ETROP study,¹² a ROP incidence of 68 % was

Figure 1. Retinopathy of prematurity (ROP) frequency and severity according to gestational age.

Figure 2. Retinopathy of prematurity (ROP) frequency and severity according to birth weight.

reported in those under 1251 g. In the United States,³⁰ an incidence of 30.9 % was found in children with weight between 750 and 999 g. In the NBs analyzed in the present study, a frequency of 37.7 % was found in children with weight ≤ 1250 g and 45.9 % in those weighing ≤ 1500 g, which is lower than that reported in India.³¹

Another factor that has been closely associated with the development of ROP is the use of oxygen. However, this remains controversial: in some studies, a higher incidence of ROP has been found with indiscriminate use of oxygen at high concentrations, in others this association has not been demonstrated.³²⁻⁴⁰ Nevertheless, rational use of oxygen is recommended in all premature

Figure 3. Retinopathy of prematurity (ROP) frequency and severity according to the time of supplementary oxygen use.

NBs, especially in the most immature. In turn, Chow²⁶ proposes that oxygen saturations should be maintained similar to fetal levels and never higher than 95% in premature newborns. In the present research, longer oxygen usage time was found to be associated with higher ROP frequency; however, the most important is oxygen saturation reached by patients, which was information that was not possible to be obtained in this research given the design of the study and the characteristics of the hospital where it was conducted, since patients who are admitted to the NICU are referred from other hospitals with a clinical summary where oxygen concentrations used or saturations reached are not recorded, only the usage time is indicated.

All patients had one or more comorbidities, with a statistically significant difference in bronchopulmonary dysplasia and intraventricular hemorrhage, with a higher frequency being observed in children with ROP, similar to that reported by Lad.³⁰ Patent ductus arteriosus and seizures were also found to be more common in them, with a statistically significant difference.

Given that ROP's nature is progression, and that timely treatment reduces the risk of visual loss, premature NBs with high risk should receive a careful examination by an experienced ophthalmologist, and all pediatricians and neonatologists looking after these premature infants should be aware of the implications of this pathology.

In developed countries, such as the United States and the United Kingdom, guidelines have been established

for the screening of these children, but it is important taking into account that each region may have different parameters in this regard, since patient characteristics and management at NICUs are different.²² These guidelines recommend screening for children ≤ 32 gestational weeks or with < 1500 g birth weight; in Mexico, technical guidelines recommend screening in NBs with gestational age ≤ 34 weeks and birth weight ≤ 1750 g.⁴¹

Children's first evaluation was found to have been carried out late according to international recommendations. According to the American Pediatrics Academy Ophthalmology section recommendation,²² children with 27 weeks' gestational age should be assessed at 31 weeks' postconceptional age or at 4 weeks' chronological age; in our study, children of that age were examined at between 31 and 44 weeks of postconceptional age and between 4 and 17 weeks of chronological age.

Very few patients (20.5 %) included in the present study underwent a second evaluation at the same hospital, and the interval between one and another was long. This could be due to a lack of resources to send the patients to the reference center, in addition to that in general or regional zone hospitals there are no human or technological resources for the care of these children, i.e., to establish timely and adequate diagnosis and treatment, as well as the required follow-up and rehabilitation. In a survey in pediatricians and neonatologists, Zepeda et al.⁴² found that the main barriers to establishing detection and effective treatment

programs are the lack of human resources, lack of access to technology and adequate equipment, lack of financial resources and institutional support, as well as the lack of knowledge about the disease.

As regards treatment, a modality instituted in this hospital is the application of paraocular dexamethasone when ROP is detected at mild stages and, later, more advanced treatments such as cryotherapy or laser are rarely required. Owing to their anti-inflammatory properties, it is possible that steroids act as antiangiogenic agents. This treatment is not referred to in the literature, and therefore evolution in the short, medium and long term of children to whom paraocular dexamethasone is administered remains to be analyzed.

Due to the increase in premature NBs survival, the incidence of ROP is expected to remain elevated; therefore we consider there's a need to conduct studies to identify the frequency of ROP in Mexico in order to establish opportune detection programs and thus provide them with the treatment and the corresponding follow-up.

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