Association of preretinal hemorrhage with the presence and severity of retinopathy of prematurity in high-risk patients

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Abstract

Objective: To assess whether preretinal hemorrhage (PRH) is associated with the presence and severity of retinopathy of prematurity (ROP) in high-risk patients. **Methods:** Prospective cohort study, patients referred to the Department of Ophthalmology for ROP screening during October-November 2016 were evaluated weekly on 4 occasions to assess the relationship with PRH and the development of ROP as well as degree of severity associated. We used absolute, median frequencies with minimum and maximum values, χ^2 test and Mann-Whitney U-test, as well as relative risk with 95% confidence interval. **Results:** A total of 30 patients, in the first week 11 females (36%) and 4 males (13%) had PRH; in the 2nd week 13 patients (43%) presented PRH and 14 (46%) developed ROP; on the 3rd week there were no changes; in the last week 8 presented HPR (26%) and 11 patients (36%) with ROP. Stage I severity occurred more frequently. Statistical significance ($p = 0.040$) was found in the presence of PRH and the development of ROP in the first week with. **Conclusions:** HPR is a risk factor for the development of ROP during the first weeks of life and is associated with stages of mild severity.

KEY WORDS: Preretinal hemorrhage. Retinopathy of prematurity. Severity.

Introduction

Retinopathy of prematurity (ROP) is defined as a progressive retinal vasoproliferative disorder that occurs exclusively in premature infants¹. Worldwide, incidences ranging from 12% to 78%, at any of its stages, are reported in children born with less than 1500-g weight²⁻⁴.

Associated systemic factors include vascular immaturity, state of hypoxia, gestational age, multiple pregnancy, respiratory distress, apnea, acidosis, bradycardia, anemia, sepsis and transfusions^{5,6}.

ROP has an international classification that considers three concentric zones that describe the retina from its posterior to the anterior portion (zone),

circumferential extension (time zone or meridians) and seriousness (stage) with presence or absence of "plus" disease:

- Zone I: with the optic disc as center, and papilla-fovea double distance, the formed circle is zone I.
- Zone II: starts at zone I border and extends nasally towards the ora serrata with the corresponding temporal area or to the equator.
- Zone III: starts at zone II border and is the remaining retinal area towards the temporal sector. It is the last zone to complete vascularization for retinal circulation full development.

ROP extension is documented according to the number of time zones involved. There are five stages:

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- Stage I or demarcation line: a demarcation line is observed between the retinal avascular and vascular areas.
- Stage II or crest: the demarcation line grows until occupying a volume, and has height and width to form a crest above the retinal plane. Small blood vessels flakes or plumes can be also observed, usually called “popcorn”, located posterior to the crest.
- Stage III or fibrovascular proliferation: extraretinal fibrovascular extending from the crest to the vitreous body is observed; it can be continuous or not, and it is localized posterior to the crest.
- Stage IV or subtotal or partial retinal detachment: partial, exudative or traction retinal detachment is observed. It is divided in A when it does not involve the macula, and B when there is.
- Stage V or complete retinal detachment: complete retinal detachment is observed, with leukocoria being clinically evident.

In addition, there are seriousness variants, such as “plus disease”, which is defined as venous dilation and arterial tortuosity of the posterior pole vasculature. The “pre-plus” disease is also a vascular alteration that manifests itself as higher-than-normal dilation and tortuosity, but less intensely than in disease plus.

Anterior progressive ROP (formerly known as “rush” disease), a rare, rapidly progressive presentation form that is observed at the posterior pole as serious plus disease and plain intraretinal neovascularization, which can easily progress to stage IV and produce total blindness if not early treated⁷. The exploration technique has to be carried out under pharmacological pupillary dilation and indirect ophthalmoscopy with 28-diopter lens. Ophthalmic dilation solutions based on cyclopentolate (0.5%) and phenylephrine (2.5%) are generally used, and are applied every 15 minutes for three times^{2,7}. The American Academy of Pediatrics establishes that infants with a birth weight of 1500 g or gestational age shorter than 30 weeks of gestation, as well as certain particular cases with birth weight of 1500-2000 g or gestational age longer than 30 weeks of gestation with unstable clinical status, should be assessed for ROP. Screening should be carried out 4 weeks after birth⁷. Once ROP has been staged, the different existing treatment should be evaluated. Cryotherapy consists in the use of a probe to freeze avascular retina areas and prevent or decrease the risk of retinopathy-secondary retinal folding or detachments; however, owing to the high risk of complications, such as inflammation, and to the need of general anesthesia in pediatric patients, it is not considered the first choice

of treatment anymore⁸. Indirect laser photocoagulation has been shown to be the first line treatment (gold standard). It consists of an indirect infrared system that produces hypoxic retina ablation turning it into anoxic retina, with a subsequent reduction of the vasogenic stimulus, the formation of abnormal vessels and disease progression⁹. Drugs that block the endothelial growth factor or anti-vascular endothelial growth factor (VEGF) are treatments that are applied by intravitreal injection¹⁰. Surgical treatment is reserved for cases of highly advanced disease, such as stages 4 and 5. Best results have been shown to be obtained at stage 4a, and the procedures that can be offered include vitrectomy and cerclage. In stage 5 cases, vitrectomy and lensectomy or open vitrectomy can be considered; however, from stage 4B on there is high risk of total visual loss after surgical management, and therefore the choice of surgery or patient follow-up and observation becomes debatable¹¹.

ROP is a pathology that is generally self-limited, with an average duration of 15 weeks encompassed from the onset of the disease until the period of its inactivation¹². Finally, the risk factors that are closely related to the development of complications, which in addition are part of the purpose of this study, include the presence of vitreous hemorrhage, and in particular preretinal hemorrhage (PRH). Retinal hemorrhage is not an uncommon finding in ROP; it has been reported at an incidence ranging from 5% to 33% in patients with any ROP stage¹³. The purpose of this study consisted in assessing whether PRH is associated with the presence and severity of ROP in high risk patients.

Method

The study was carried out in premature infant patients seen at the Ophthalmology Department of the No.25 High-Specialty Medical Unit (UMAE – *Unidad Médica de Alta Especialidad*) of the Mexican Institute of Social Security, in Monterrey, Nuevo León, for ROP screening during October and November 2016. Premature patients with less than 30 weeks of gestation at birth and with more than 30 days of having been born at assessment, with low weight for gestational age below 1500 g, and with risk factors for ROP, such as use of oxygen therapy, were included. The study underwent evaluation by the medical unit ethics committee and its authorization was obtained, in addition to obtaining informed consent for pediatric patient authorized and signed by the legal guardian of each patient. Four weekly assessments were carried out for fundus exploration under

Table 1. Clinical characteristics of 30 premature infant patients according to the presence of PRH at study's first assessment

	Total (n = 30)	PRH		p
		Yes (n = 15)	No (n = 15)	
Gender				
Male	9 (30%)	4 (13%)	5 (16%)	0.028
Female	21 (70%)	11 (36%)	10 (33%)	
Age (days)	33 (30-39)	34 (30-38)	33 (31-39)	0.539
Gestational age (weeks)	28 (27-30)	28 (27-30)	29 (27-30)	0.967
Birth weight (g)	1067 (645-1725)	945 (645-1725)	1100 (910-1425)	0.098
Oxygen therapy (days)	27 (14-35)	23 (14-35)	28 (21-35)	0.081

Values presented as absolute frequencies (percentages) and medians (minimum-maximum).

Table 2. Association of PRH at first study week with the presence of ROP in the following 3 weeks in 30 premature infant patients

	Total (n = 30)	PRH at first week		RR (95% CI)	p
		Yes (n = 15)	No (n = 15)		
ROP					
Week 2	23 (76%)	14 (46%)	9 (30%)	1.55 (1.00-2.40)	0.040
Week 3	25 (83%)	14 (46%)	11 (36%)	1.27 (0.91-1.77)	0.165
Week 4	17 (56%)	11 (36%)	6 (20%)	1.83 (0.91-3.65)	0.070

Values presented as absolute frequencies (percentages), medians (minimum-maximum), relative risk with 95% CI and P value calculated with the Chi-square test.

PRH: preretinal hemorrhage; ROP: retinopathy of prematurity; 95% CI: 95% confidence interval.

pharmacologic dilation using tropicamide (0.8%) and phenylephrine (0.5%), applied every 15 minutes for three times. Two groups were obtained: one first group of patients who had PRH without ROP, and a second group without PRH or ROP at first assessment. Findings obtained at the second, third and fourth weeks were observed and recorded, comparing the presence of PRH, ROP and severity thereof, in addition to the indicated treatments in the cases where they were required. For statistical analysis of the results, absolute frequencies and percentages were measured, as well as means or medians; the chi-square test was used for qualitative variables, Student's t-test and Mann-Whitney U-test were used for independent samples, and for the magnitude of association, the relative risk was measured with its 95% confidence interval. A p-value < 0.05 was considered to be statistically significant. The SPSS statistical package, version 17.0, was used.

Results

The study was carried out at the No. 25 UMAE of Monterrey during the months of October and November 2016. Thirty premature patients attending for ROP screening assessment were included, out of which 21 were girls (70%) and 9 were boys (30%); in addition, 376% of females and 13% of males had PRH, with a p-value of 0.028 and a statistically significant relationship

between the presence of PRH and patient gender. Median age at assessment was 33 days (range: 30-39), average gestational age was 28 weeks (range: 27-30), average birth weight was 1067 g (range: 645-1725) and average oxygen therapy time was 27 days (range: 14-35) (Table 1).

In the second assessment, a decrease in the incidence of PRH of up to 43.3% was observed. The development of ROP in 23 patients (76.7%) was also evident, with a p-value of 0.04 being obtained, with statistical significance. In addition, 19 patients (63.3%) had seriousness stage I and 4 patients (13.3%) stage II. At third assessment, the percentage of PRH was not changed and the occurrence of ROP was observed in 25 patients (83.3%), with p = 0.165, without the percentage of seriousness stage I being modified and with the number of patients with stage II increasing to 5 (17.7%), as well as 1 patient with stage III (3.3%), which was the highest seriousness level observed during the study. Finally, on the fourth week, PRH was observed in 8 patients (26.7%), with a p-value of 0.018, demonstrating a decrease and resolution in a considerable number of cases in comparison with the study initiation. Seventeen patients (56.7%) continued with ROP, with predominance of stage I in 11 of them (36.7%), 9 patients (30%) without ROP with avascular retina and, notoriously, 4 (13.3%) without ROP with vascularized and fully mature retina (Table 2).

Relative risk with regard to the presence of PRH and to the development of ROP was analyzed. In the second week, the relative risk for developing ROP having presented PRH was 1.55 (1.0-2.4), which represented a significant result. Finally, on the fourth week, the relative risk for PRH was 1.83 (0.91-3.65) (Table 2).

The patients who presented with stage I and II ROP were assessed weekly without receiving medical or surgical treatment. Those at stage III required medical management with intravitreal antiangiogenic agents and close weekly follow-up. Patients with avascular retina without ROP were assessed every 15 days, and those with vascularized retina were discharged. No patients presented with stages IV or V during the study, and treatment with photocoagulation, cryotherapy or surgery was therefore not necessary.

Discussion

ROP is a condition that is exclusive of premature infants and that manifests itself by a progressive vasoproliferative disorder that generally resolves itself completely; however, there are serious cases that experience important sequels that compromise patient visual function and prognosis, such as vitreous hemorrhage, retinal detachment, neovascular glaucoma and ptosis bulbi, which culminate in an important visual limitation or blindness^{7,8}.

ROP occurs with higher prevalence in developing countries, representing an important public health problem. It has a variable global incidence, from 12% to 78% of newborns meeting the screening criteria⁴. The importance of screening is reflected in opportune diagnosis and treatment, especially in those infants at initial stages that have not yet developed complications. This screening test should be carried out in every patient with at least 30 days of extrauterine life, with a gestational age shorter than 30 weeks and birth weight lower than 1500 g⁷. Gestational age of less than 30 weeks, birth weight lower than 1500 g and oxygen therapy are the factors mainly associated with the occurrence of this pathology^{7,8}.

The main objective of this study was to compare the presence of PRH in the assessed patients and the relationship that exists with the development of ROP and its seriousness. Vitreous hemorrhage has been recognized as an initial risk factor for the development and progression of ROP since 1913 by Oguchi¹⁴. Different studies have been conducted in order to explain the vitreous hemorrhage pathophysiology in ROP

natural evolution, such as the one by Cleary and Ryan¹⁵, who demonstrated the role of intraocular blood in the development of proliferative retinopathy after penetrating surgery. Ehrenberg et al.¹⁶ confirmed that pathologic changes occurred even without a previous history of penetrating surgery. Hutcheson et al.¹⁵ reported in their study an incidence of only 3% in the assessed infants, but that nevertheless progressed to a borderline high risk stage of disease. So far, no studies comparing the presence of PRH as a risk factor associated with the development of ROP have been reported, which is why carrying out this work was decided. Among the results obtained in the present study, the incidence of PRH was observed to have values of 43.3% at first assessments and to be reduced down to 26.7% by the fourth week; still, it had a statistically significant value, contrasting with the results obtained by Hutcheson for vitreous hemorrhage. The incidence of ROP was 76.6% at second week, which was regarded as a statistically significant value, with variations throughout the following weeks and showing a final value of 56.7% in terms of incidence, with statistically non-significant values. Therefore, the presence of PRH constitutes a risk factor for the onset and development of ROP at initial phases of the disease.

Another objective was to investigate the existing association between the presence of ROP and its seriousness. Stage I was observed to occur more commonly, with a value that ranges from 63.3% initially to 36.7% at week 4, followed by the presence of avascular retina with no data consistent with ROP in 23.3% to 30% of total assessed patients at the end of the 4 weeks, with the presentation of stage III standing out as the most serious in 13.3% of cases. On the other hand, in 13.3% of patients there was favorable progression until the retina was observed to be free of alterations and with full vascularization, with discharge from the screening program being achieved without further complications. There is considerable difference with the results obtained by Hutcheson et al. in their study, where the majority of patients with vitreous hemorrhage evolved to advanced stage IV and subsequently to retinal detachment.

The criteria for ROP treatment are currently well established and were assessed in the present study⁸. Throughout the work, a weekly evaluation was performed in order for the fundus examination findings to be determined, as well as the indicated treatment in case it was required. At the beginning of the study, 100% of infants were found to have an immature and

avascular retina on fundus examination; average age at screening was 33 days of life. At week 2, there was an important change, with ROP being found in 76.7%, which were classified as stages I and II, without requiring treatment. At third and fourth weeks, progression was evident in four patients who progressed to stage III, and starting medical treatment by applying intravitreal antiangiogenic agents became imminent, with tight follow-up every week was indicated. As previously mentioned, Huthcheson et al. reported that most their patients with vitreous hemorrhage and ROP progressed to stage IV with retinal detachment, and were managed with vitrectomy. Finally, it should be mentioned that, at the end of the study, four patients were discharged from the screening program after demonstrating a favorable response when retinal vascularization was observed, without further need of subsequent follow-up, demonstrating that this pathology resolves in weeks, at an average of 16 weeks after diagnosis.

Conclusions

The presence of PRH is significantly associated with the development of ROP and is an independent risk factor for the development of the disease within the first weeks of life; subsequently, it develops even without the presence of PRH, most probably because of other factors.

ROP seriousness manifests itself with mild stages in most cases, without medical treatment or surgical intervention being required, with weekly follow-up, representing a visual prognostic factor that is favorable to the patient.

It is confirmed that, due to its natural evolution, ROP resolves in weeks after diagnosis, and favorably in most cases. In addition, the importance of continuing with the screening at the age established by international ROP guidelines is made evident, in order to decrease the risk of progression, to be able to establish a diagnosis and opportune treatment, and this way avoid complications that affect patient visual

prognosis, as well as personal and socioeconomic implications for the patient in the future.

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Conflict of interests

There are no conflicts of interests to declare.

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