www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2017;6(1):e060122
doi: 10.7363/060122
Received: 2016 Apr 12; revised: 2016 Jul 17; rerevised: 2016 Jul 19; accepted: 2016 Jul 22; published online: 2017 Jan 05

Original article

Retinopathy of prematurity: results from 10 years in a single neonatal intensive care unit

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Abstract

Introduction: Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina of preterm newborns and is an important and preventable cause of visual impairment in childhood. This study aimed to assess the incidence and main risk factors associated with the development of ROP in the last 10 years at Hospital Prof. Doutor Fernando Fonseca in Lisbon, Portugal.

Methods: Observational and retrospective study conducted between 2005 and 2014 at Hospital Prof. Doctor Fernando Fonseca. The study included newborns of gestational age < 32 weeks. We analyzed maternal, prenatal and neonatal factors associated with the development of ROP. Statistical analysis were performed with Statistical Package for Social Sciences (SPSS®) software. Univariate and multivariate analyses were performed and a multiple logistic regression model was carried out with a significance level $\alpha = 0.05$.

Results: 527 premature infants with a gestational age < 32 weeks were studied, of which 165 developed ROP. 60 of these patients needed treatment. In the univariate analysis, the risk factors for the development of ROP were maternal infection in pregnancy, low birth weight, low gestational age, low Apgar score at 5 minutes, need for oxygen therapy until the 28th day of life, a high score on the CRIB and SNAPPE2 scales, use of surfactant, respiratory distress syndrome, persistence of patent ductus arteriosus, peri-intraventricular hemorrhage and neonatal sepsis. In the multiple logistic regression analysis, risk factors for ROP were the presence of neonatal sepsis, respiratory distress syndrome, persistence of patent ductus arteriosus and a high score on the neonatal SNAPPE2 scale.

Conclusions: We found a ROP incidence rate of 31.3%, with risk factors similar to those observed in other studies.

Keywords

Prematurity, retinopathy, risk factor, incidence.

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How to cite

Coutinho I, Pedrosa C, Mota M, Azeredo-Lopes S, Santos C, Pires G, Teixeira S, Cunha M. Retinopathy of prematurity: results from 10 years in a single neonatal intensive care unit. J Pediatr Neonat Individual Med. 2017;6(1):e060122. doi: 10.7363/060122.

Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative change secondary to inadequate vascularization of the retina of preterm newborns. It was first described as retrolental fibroplasia by Terry in 1942.

ROP is an important and preventable cause of poor vision in children, with 6-18% of cases of blindness occurring in developed countries being directly attributable to ROP [1, 2]. Despite the increased survival of premature infants with low gestational age and low birth weight, recent studies have shown a decrease in the incidence of ROP, which can be due to improved neonatal care and better understanding of the disease [3].

The pathophysiology of this disease is still not fully understood. Over the past 50 years, some studies have been performed in order to identify possible factors associated to the development of ROP. It is known that the retinal vasculature begins to develop from the optic disc to the periphery around the 16th week of gestation, with vascularization of the nasal region occurring around 32-36 weeks and the temporal region at 40-42 weeks [4]. Thus, the degree of prematurity of the newborn determines the stage of retinal vasculature maturation and the affected zone [5].

Oxygen tension is low *in utero* and the extra-uterine environment is hyperoxic for premature infants. After birth and until 30 weeks post conceptional age, retinal vascularization is inhibited because of hyperoxia and loss of growth factors provided at the maternal-fetal interface like IGF-1. However, as the newborn grows, the avascular retina becomes more metabolically active, which leads to tissue hypoxia, stimulating pro-angiogenic factors (VEGF and IGF-1) and leading to retinal neovascularization between 32 and 34 weeks post-conceptional age [5, 6].

Several risk factors have been associated with the development of ROP, most commonly gestational age and birth weight. Other potential risk factors described in the literature are male gender, oxygen therapy, apnea, sepsis, peri-intraventricular hemorrhage, patent ductus arteriosus, anemia and blood transfusion, although the impact of these factors on the progression of the disease is not fully understood [1, 5, 7-9]. By contrast, preeclampsia [10] and lung maturation induced by prenatal steroids therapy have been suggested as protective factors.

Screening for ROP is critical to control visual sequelae. Infants with a birth weight < 1,500 g or gestational age < 32 weeks are groups considered at high risk, in which eye screening should be carried out. This screening can be extended to other children with co-morbidities associated with ROP as indicated by the neonatologist [8, 11-13]. Ophthalmologic screening occurs between 4-6 weeks of age or between 31-33 weeks post-conceptional age, with preference for a later date [8, 11-13].

The disease is classified according to the international classification (ICROP) (**Tab. 1**).

Current treatment criteria are summarized in **Tab. 2** and are based on the CRYOP-ROP and ETROP studies. Most cases of ROP resolve spontaneously without sequelae between 32 and 42 week of gestation [5, 6]. Currently, laser photocoagulation of the avascular retina is the treatment of choice, and various studies show that its functional and structural results are superior to cryotherapy [14].

The intravitreal injection of anti-VEGF appears to be another promising option for the treatment of ROP, and encouraging results have been presented, such as those in the BEAT-ROP study. It is a relatively quick and easy treatment to perform and it is associated with a lower rate of myopia than laser therapy, however more controlled studies are necessary to evaluate its long-term safety.

Its use, isolated or in combination with laser therapy, is currently restricted to cases of aggressive posterior ROP, ROP stage 3 in zone I, in the presence of local complications such as media opacity or poor dilation, in patients whose use of laser therapy is contraindicated because of clinical instability, in ROP stages 4 or 5 before a vitrectomy and in cases in which laser therapy fails [4, 15].

Vitrectomy is another therapeutic option available for the advanced stages of ROP, associated with retinal detachment.

Table 1. International classification of retinopathy of prematurity.

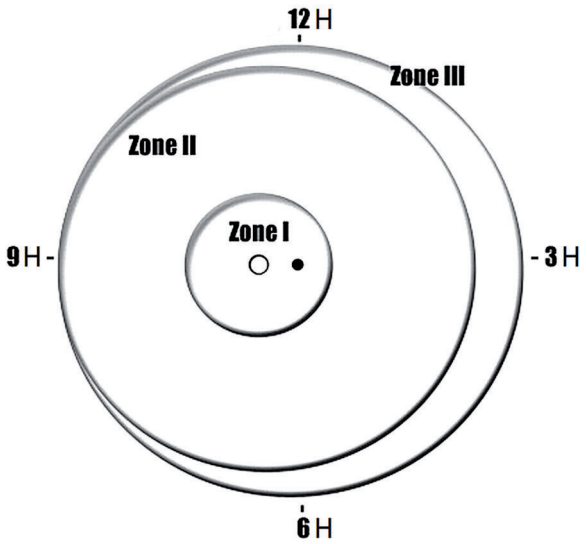
<table>
<tr><th>Stage</th><th>Localization</th><th>Extension</th></tr>
<tr><td>Stage 1 – flat demarcation line</td><td rowspan="2">Zone I – circle area centered on the optic nerve with a radius twice the distance from the optic nerve to the macula</td><td rowspan="5">Evaluation in hours
 
</td></tr>
<tr><td>Stage 2 – high crest between the vascularized and non-vascularized retina</td></tr>
<tr><td>Stage 3 – fibrovascular proliferation</td><td>Zone II – it extends from the end of Zone I to the nasal ora serrata</td></tr>
<tr><td>Stage 4 – partial detachment of the retina</td><td rowspan="2">Zone III – it corresponds to the growing remaining crescent area</td></tr>
<tr><td>Stage 5 – full detachment of the retina</td></tr>
<tr><td>Plus disease</td><td colspan="2">Vascular dilatation and tortuosity in the posterior pole
Gravity signal and progression, which may arise at any stage
Reflects an increase in VEGF1</td></tr>
</table>

Table 2. Treatment indications.

Threshold ROP Classical indication for treatment according to the CRYO-ROP 1988 study	• Stage 3 in Zone II, at least 5 hours or 8 hours continuous extension interspersed in the presence of plus disease in Zone I
Pre-threshold ROP Type 1 Indication for treatment according to the ET-ROP study	• Any stage of ROP in Zone I, with plus disease • Stage 3, Zone I, without plus disease • Stage 2 or 3, Zone II, with plus disease
Aggressive posterior ROP Definition introduced in the international classification of 2005	• Unusual, severe and progresses rapidly • Zone I or II with plus disease that does not follow a pattern according to development stage

Considering that the incidence and risk factors for ROP vary from region to region, the present study aimed to analyze the situation in our hospital in the last 10 years.

Methods

This was an observational and retrospective study regarding patients admitted between 2005 and 2014 at the Hospital Prof. Doutor Fernando Fonseca. The study included infants with a gestational age < 32 weeks who survived and had neonatal and ophthalmologic complete clinical registration for the variables under study. Ophthalmologic screening was performed by an experienced ophthalmologist, according to the timetable and procedures proposed by national and international guidelines for the screening of ROP.

The maternal variables analyzed were maternal age, multiple pregnancy, pre-eclampsia, infection (chorioamnionitis or TORCH) and prenatal use of steroids. Neonatal variables were gestational age, birth weight, sex, Apgar score at 5 minutes, respiratory distress syndrome, use of surfactant, oxygen therapy until the 28th day after birth, peri-intraventricular hemorrhage, neonatal sepsis, CRIB and SNAPPE2 scores and persistence of patent ductus arteriosus.

Statistical analysis of the data was performed using SPSS®. Multiple logistic regression models were used, initially considering the explanatory variables obtained by univariate analyses.

Student's t-test and the Chi-squared test were used when applicable or, alternatively, Fisher's exact test was used. Mann-Whitney test was also used. Difference were considered statistically significant when $\alpha = 0.05$.

Results

Between 2005-2014, 35,210 children were born, of whom 705 (2%) had a gestational age of less than 32 weeks. Of the 705 infants, 178 were excluded due to neonatal death or incomplete ophthalmic medical records. Thus, the sample of our study consisted of 527 infants with a gestational age of less than 32 weeks. Of the 527 infants, 258 (49.0%) were male, mean gestational age was 29 weeks and the average birth weight was 1,137 g. The sample under study was divided into two groups with and without ROP; the main population characteristics are summarized in **Tab. 3**. The ROP group had a mean gestational age of 26.8 weeks and average birth weight of 882 g. In the group without ROP, mean gestational age was 30 weeks and average birth weight was 1,252 g.

The risk factors considered to be significant for ROP development in the univariate analyses (**Tab. 3**) were low birth weight, low gestational age, low Apgar score at 5 minutes, need for oxygen therapy

Table 3. Sample characteristics and results of univariate logistic regression models.

Variable	Preterm newborns with ROP (n = 165)	Preterm newborns without ROP (n = 362)	Univariate analysis	
			p-value	OR
Maternal age (years), mean ± std. deviation	30.02 ± 5.86	29.74 ± 6.74	0.647	1.007
Pre-eclampsia, No / Yes	150 / 15	325 / 37	0.750	(ref = "No") 0.903
Infection in pregnancy, No / Yes	150 / 15	346 / 16	**0.032**	(ref = "No") 2.219
Twin pregnancy, No / Yes	131 / 34	292/ 70	0.639	(ref = "No") 1.116
Prenatal steroids, No / Partial / Complete	18 / 48 / 99	44 / 119 / 199	0.681	(ref = "No") 0.986 1.169
Birth weight (g), mean ± std. deviation (min; max)	882 ± 263 (415; 1,835)	1,252 ± 287 (550; 2,000)	**< 0.001**	0.995
Gestational age (days), mean ± std. deviation	188 ± 14 26.8 weeks	209 ± 14 30 weeks	**< 0.001**	0.909
Male / Female	78 / 87	180 / 182	0.790	(ref = "Female") 0.951
Apgar at 5 min, median (min; max)	7.8 (2; 10)	8.38 (0; 10)	**< 0.001**	0.763
Oxygen therapy until the 28th day of life, No / Yes	38 / 127	272 / 90	**< 0.001**	(ref = "No") 8.194
Surfactant use, No / Yes	33 / 132	187 / 175	**< 0.001**	(ref = "No") 4.480
Respiratory distress syndrome, No / Yes	14 / 151	105 / 257	**< 0.001**	(ref = "No") 4.74
Persistence of ductus arteriosus, No / Yes	70 / 95	270 /92	**< 0.001**	(ref = "No") 4.115
Peri-intraventricular hemorrhage, No / Yes	97 / 68	277 / 85	**< 0.001**	(ref = "No") 2.342
Neonatal sepsis	118	143	**< 0.001**	(ref = "No") 3.907
Gram positive	42	51		
Gram negative	26	23		
Fungal	11	6		
Others	39	63		
CRIB, median (min; max)	4 (0; 14)	1 (0; 18)	**< 0.001**	1.358
SNAPPE2, median (min; max)	39 (0; 85)	20 (0; 101)	**< 0.001**	1.036

Min: minimum; max: maximum; ref: reference; std: standard.

until the 28th day after birth, higher value of CRIB and SNAPPE2 score, peri-intraventricular hemorrhage, patent ductus arteriosus, use of surfactant, respiratory distress syndrome, maternal infection during pregnancy and neonatal sepsis. There was no statistically significant difference between the two groups (with and without ROP) in terms of sex, maternal age, twin pregnancy, preeclampsia or the use of antenatal steroids.

It was also observed that birth weight and gestational age were correlated with a Spearman correlation coefficient of 0.773 ($p < 0.001$), so they should not be used together in the same model to avoid collinearity. Thus, when considered separately, each increase of 1 week in the gestational age provided a reduction of approximately 9% in the chance of developing ROP (OR = 0.909, $p < 0.001$). In turn, for each increase of 1 gram in birth weight, there was a decrease of about 0.5% in the risk of ROP (OR = 0.005, $p < 0.001$), i.e., for each increase of 10 g, there was a decrease in ROP risk of about 5%.

It was also observed that when the relationship between the occurrence of ROP and the variables weight and gestational age was adjusted by the effect of other covariates, the latter never exhibited statistically significant results. It can therefore be concluded that both gestational age and birth weight "cancel" statistical significance of other factors. Therefore, the effect of other possible factors were analysed when both weight and gestational age were not considered. The multivariate logistic regression model has found four risk factors: neonatal sepsis (OR = 2.287, $p < 0.001$), higher value of SNAPPE2 (OR = 1.023, $p < 0.001$), respiratory distress syndrome (OR = 2.076, $p = 0.027$) and persistence of ductus arteriosus (OR = 1.932, $p = 0.004$) (**Tab. 4**). Although multivariate method is the preferred method to study this multifactorial disease, the results can be unstable on many occasions with the influence of one variable on others [3].

The incidence of ROP during this time period was 31.3% (n = 165). As for the stage, 59 infants (35.76%) developed ROP at stage 1, 61 newborns (36.97%) at stage 2, 43 infants (26.06%) at stage 3 and 2 newborns (1.21%) at stage 4. There were no cases of ROP stage 5 (**Tab. 5**). The association between different parameters and the severity of ROP is described in **Tab. 5**. The severe stages of ROP (stages 3, 4 and 5) were associated with lower birth weight, lower gestational age and increased oxygen therapy. The average birth weight and gestational age associated with severe ROP were 761 g and 27 weeks, respectively.

Of the 165 infants with ROP, 60 (36.36%) required treatment, with spontaneous remission of the disease in the other cases. Laser therapy was performed on 50 patients, while 10 patients received bevacizumab injection.

Discussion

In our study the incidence of ROP was 31.3%, a result that is similar to many other studies with similar selection criteria [16-18] and performed in developed countries. However, some studies showed lower incidence rates [19-23].

The risk factors we observed were similar to those described in the literature [9, 13, 22].

A low value of the Apgar score at 5 minutes and a high value of the CRIB and SNAPPE2 scores are indicators by themselves of morbidity and mortality in infants. It is known that ROP mainly affects the weakest newborns, although it is not fully understood if the most severe stages

Table 4. Sample characteristics and results of the multiple logistic regression models.

Variable	Preterm newborns with ROP (n = 165)	Preterm newborns without ROP (n = 362)	Multivariate analysis	
			p-value	OR
Respiratory distress syndrome, No / Yes	14 / 151	105 / 257	**0.027**	2.076
Persistence of ductus arteriosus, No / Yes	70 / 95	270 / 92	**0.004**	1.932
Neonatal sepsis	118	143	**< 0.001**	2.287
Gram positive	42	51		
Gram negative	26	23		
Fungal	11	6		
Others	39	63		
SNAPPE2, median (min; max)	39 (0; 85)	20 (0; 101)	**< 0.001**	1.023

Table 5. ROP incidence by stage of disease and results of the Chi-square test (or Fisher's exact test) and Mann-Whitney test.

Parameter	Stage 1+2 (n = 120)	Stage 3+4+5 (n = 45)	p-value
Pre-eclampsia			0.241
No	111	39	
Yes	9	6	
Infection in pregnancy			0.076
No	38	8	
Yes	82	37	
Birth weight			**< 0.001**
< 1,000 g	98	43	
1,000-1,499 g	21	2	
1,500-2,499 g	1	0	
> 2,500 g	0	0	
Gestational age			**0.004**
< 189 days (< 27 weeks)	64	35	
190-224 days (27-32 weeks)	56	10	
Apgar at 5 min, mean ± std. deviation	7.82 ± 1.39	7.73 ± 1.56	0.977
Oxygen therapy until the 28th of life			**0.007**
No	36	4	
Yes	84	41	
Surfactant use			0.080
No	28	5	
Yes	92	40	
Respiratory distress syndrome			0.355
No	12	2	
Yes	108	43	
Persistence of ductus arteriosus			0.493
No	52	17	
Yes	68	28	
Periventricular hemorrhage			0.220
No	74	23	
Yes	46	22	
Neonatal sepsis			0.076
No	38	8	
Yes	82	37	
SNAPPE2, mean ± std. deviation	38.11 ± 21.99	41.45 ± 18.60	0.457

of the disease are associated with the severity of co-morbidities resulting from prematurity or therapeutic interventions necessary to maintain life [24, 25].

The presence of peri-intraventricular hemorrhage, persistence of patent ductus arteriosus, maternal infection, oxygen therapy until the 28th day after birth and respiratory distress syndrome relate to and allow ischemia to occur, therefore increasing the need for supplemental oxygen and leading to injury of immature capillaries, generation of free radicals, vascular obliteration and ultimately neovascularization. In this regard, several studies suggested the importance of avoiding SaO_2 > 92-95% and fluctuations in oxygen saturation [26-28].

The use of surfactant is associated with decreased mortality and morbidity of premature infants, but its role in the development of ROP is controversial; most studies have shown that surfactant use does not reduce the incidence of ROP but rather decreases its severity. In our study, the use of surfactant was associated with the

development of ROP (the risk of ROP in a child that received surfactant was about 4.5 times higher that of a child not given surfactant; OR = 4.480, p < 0.001, **Tab. 3**). This could be attributed to the greater clinical instability of newborns who were treated with surfactant [29]. Moreover, the use of surfactant did not have a significant impact in reducing the severity of ROP (**Tab. 5**).

Neonatal sepsis was observed to be as a risk factor, possibly in relation to its inflammatory effect, which can stimulate retinal neovascularization [5, 30-32].

Unlike in other publications, male gender was not a risk factor for the development of ROP in the present study [24].

Another interesting fact is that prenatal steroid administration did not reduce the risk of ROP, which is concordant with other studies [9], despite having a positive impact on the survival of premature infants and reducing the incidence of respiratory distress syndrome. Moreover, preeclampsia was not a protective factor in the current cohort although it has been previously described as protective against ROP in other studies [10].

As the present study was of retrospective design, it was not possible to analyze other causes described as important risk factors to ROP.

Conclusions

The pathogenesis of ROP is multifactorial. In this study the most significant risk factors to development of ROP were low birth weight, low gestational age, low Apgar score at 5 minutes, need for oxygen therapy until the 28th day after birth, a high score on CRIB and SNAPPE2 scales, use of surfactant, respiratory distress syndrome, persistence of patent ductus arteriosus, peri-intraventricular hemorrhage, maternal infection and neonatal sepsis.

The incidence of ROP was 31.3% and severe ROP (stage 3 or greater) was 27.27%. A treatment was performed in 36.36% of ROP cases.

ROP remains a major complication in premature newborns despite all the advances that have been made in recent years.

Excellence in pre- and neonatal care, screening and early treatment of ROP are keys to prevent vision loss induced by this disease. It is mandatory to ensure that these newborns have regular ophthalmologic support, as they are more likely to have other ocular complications such as refractive defects (myopia, astigmatism and anisometropy), oculomotor balance disorders (strabismus) and amblyopia [5, 6, 30].

Acknowledgements

A special thanks to the neonatology staff at Hospital Prof. Doutor Fernando Fonseca for all assistance provided.

Declaration of interest

The Authors have no conflicts of interest relevant to this article.

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