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Research Article

The Prevalence of Retinopathy of Prematurity and Relationship with Gestational Age and Birth-Weight; Contributing to Screening Programmes

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Abstract

Objective: To determine the incidence of retinopathy of prematurity ROP) and the risk factors especially gestational age (GA) and birth weight (BW) associated with its development and to contribute to screening criteria.

Design: A Randomized, retrospective study.

Setting: Adana Numune Research and Training Hospital, Adana, Turkey.

Subjects: Three hundred eighty-two consecutive infants were included in the data analysis. BW and GA were evaluated according to the development of ROP.

Intervention: Study group was included premature infants who were 37 gestational weeks or younger.

Main Outcome Measures: Detection of ROP disease, stage of the ROP disease and relationship with GA and BW of the disease.

Results: ROP was detected in 133 infants (35%) of 382 infants; of those 58% had stage 1 disease, 10% had stage 2 disease, 22% had stage 3, 2% had stage 4a, 1% had stage 4b, 1% had stage 5 and 8% had aggressive posterior retinopathy of prematurity disease. Low BW and low GA was statistically associated with ROP.

Conclusions: ROP is known to be a multifactorial disease. The incidence of retinopathy of prematurity in premature infants is 35%. Major risk factors are low GA and low BW.

Keywords: *Retinopathy of Prematurity; Risk Factors; Screening Criteria; Incidence*

Abbreviations

ROP: Retinopathy of Prematurity; GA: Gestational Age; BW: Birth Weight

Introduction

Retinopathy of prematurity (ROP) is a proliferative retinopathy which is the preventable common cause of the blindness in preterm infants. Detection and treatment of the ROP have become more important because the progression of the disease is very quick. It has several risk factors but the most important risk factors are low gestational age (GA) and low birth weight (BW) [1]. A lot of screening guidelines have been based on these factors to identify infants needing examination.

The incidence of the ROP is different in countries. In developed countries, ROP-associated blindness incidence has been reported to be lower than 10% of extremely preterm born children but in middle-income countries, the incidence is greater than 40% [2-4].

In this retrospective study, we analyzed the incidence of ROP. We aimed to contribute to screening programmes.

Subjects and Methods

Approval was obtained from the local ethics committee for the study. The study conformed to the tenets of the Declaration of Helsinki.

In this retrospective study, we examined 382 premature infants who were born with GA ≤ 37 weeks at our hospital and referred from other hospitals, Adana, Turkey.

Exclusion criteria were lethal congenital anomalies, death before examination, death or loss to follow up before complete retinal vascularization was developed and incomplete screening procedure.

The first ophthalmological examination was performed by an experienced ophthalmologist with indirect ophthalmoscope at 4 weeks after birth (GA ≥ 27 weeks) or 31 weeks of corrected GA (GA ≤ 27 weeks). The pupil was dilated with tropicamide 0.5% and phenylephrine 1%. Ophthalmologist used 20D and 28D lenses, sterile lid speculum and scleral depressor.

ROP was classified according to the international classification of ROP and screening procedure was designed in accordance with suggestions of the American Academy of Pediatrics, American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus. The diagnosis of severe ROP is defined as threshold and type 1 pre-threshold ROP. The Early Treatment for Retinopathy of Prematurity (ETROP) study results recommended treating ROP with laser photocoagulation. In zone II or III cases, we preferred laser treatment. In zone I or posterior zone II cases, we preferred anti-VEGF. The babies were followed up until full retinal vascularization was observed.

Infants were classified into 4 groups according to GA; < 28 week, 28 - 31 weeks, 32 - 34 weeks, 35 - 37 weeks. Infants also classified into 8 groups according to the BW; ≤ 750g, 751 - 999g, 1000 - 1249g, 1250 - 1499g, 1500 - 1749g, 1750 - 1999g, 2000 - 2499g, ≥ 2500g.

Data analysis was conducted using SPSS V.20.0 (SPSS Inc., Chicago, IL). Chi-square test was used to analyze qualitative variables. A difference with $p < 0.05$ was considered significant.

Results

During the study period, a total number of 382 preterm infants (222 female (58%) and 160 male (42%)) with ≤ 37 week of GA were assessed. Mean GA was 31.9 ± 2.1 weeks (range: 25 - 37 weeks) and mean BW was 1575.4 ± 495.2g (range: 690 - 4050g).

The overall incidence of ROP was 35% (133/382). 77 infants (58%) had stage 1, 13 infants (10%) had stage 2, 29 infants (22%) had stage 3, 4 infants (0.03%) had stage 4 and 5 of the disease and 10 infants (0.07%) had aggressive posterior retinopathy of prematurity (APROP). Mean GA who had any stage of the disease was 30.1 ± 2.1 weeks (range: 24 - 35.9 weeks) and mean BW was 1263.6 ± 390.2g (range: 690 - 3190g).

The incidence of ROP in female and male infants were 39% (86/222), 29% (47/160), respectively. There was no significant difference between genders (p = 0.065).

The incidence of ROP in GA with < 28 week was 100%, 28 - 31 weeks was 63%, 32 - 34 weeks was 15%, 35 - 37 weeks was 13%. The incidence rate of the disease was increased with the decrease in the GA (p < 0.001) (Table 1).

Variables	ROP	No ROP	P
	Number (%)	Number (%)	
Gender			
Female	86 (39)	136 (61)	0,065
Male	47 (29)	113 (71)	
Gestational age (weeks)			< 0,001
< 28 weeks	22 (100)	0 (0)	
28 - 31 weeks	76 (63)	44 (37)	
32 - 34 weeks	25 (15)	138 (85)	
35 - 37 weeks	10 (13)	67 (87)	
Birth weight (g)			< 0,001
< 750 g	3 (100)	0 (0)	
750 - 999g	21 (91)	2 (9)	
1000 - 1249g	22 (71)	9 (29)	
1250 - 1499g	23 (44)	29 (56)	
1500 - 1749g	28 (37)	48 (63)	
1750 - 1999g	19 (29)	47 (71)	
2000 - 2499g	8 (11)	68 (89)	
> 2500g	9 (16)	46 (84)	

Table 1: *Comparison of characteristics features of ROP (+) and ROP (-) infants.*

ROP: Retinopathy of Prematurity.

The incidence of the ROP in BW with < 750g was 100%, 750 - 999g was 91%, 1000 - 1249g was 71%, 1250 - 1499g was 44%, 1500 - 1749g was 37%, 1750 - 1999g was 29%, 2000 - 2449g was 11%, > 2500g was 16%. The incidence rate of the disease was increased with the decrease in the BW ($p < 0.001$) (Table 1).

The incidence of the stage of the ROP according to the gestational age and birth weight are shown in table 2.

Variables	Stage of ROP							P
	Stage 1	Stage 2	Stage 3	Stage 4a	Stage 4b	Stage 5	APROP	
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	
Gender								
Female	48 (56)	10 (12)	19 (22)	1 (1)	1 (1)	1 (1)	7 (8)	0,940
Male	29 (62)	4 (9)	10 (21)	1 (2)	0 (0)	0 (0)	3 (6)	
Gestational age (weeks)								
< 28 weeks	7 (32)	4 (18)	7 (32)	1 (5)	0 (0)	0 (0)	3 (13)	0,018
28 - 31 weeks	45 (59)	8 (11)	16 (21)	1 (1)	0 (0)	1 (1)	6 (8)	
32 - 34 weeks	18 (69)	1 (4)	5 (19)	0 (0)	1 (4)	0 (0)	1 (4)	
35 - 37 weeks	7 (78)	1 (11)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	
Birth weight (g)								
< 750g	0 (0)	0 (0)	2 (67)	0 (0)	0 (0)	0 (0)	1 (33)	0,038
750 - 999g	9 (43)	3 (14)	6 (29)	1 (5)	0 (0)	0 (0)	2 (10)	
1000 - 1249g	11 (50)	4 (18)	4 (18)	0 (0)	0 (0)	1 (5)	2 (9)	
1250 - 1499g	15 (63)	3 (13)	5 (21)	0 (0)	0 (0)	0 (0)	1 (4)	
1500 - 1749g	15 (54)	0 (0)	10 (36)	0 (0)	0 (0)	0 (0)	3 (11)	
1750 - 1999g	17 (90)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	
2000 - 2499g	4 (57)	1 (14)	0 (0)	1 (14)	1 (14)	0 (0)	0 (0)	
> 2500g	6 (67)	1 (11)	2 (22)	0 (0)	0 (0)	0 (0)	0 (0)	

Table 2: *Retinopathy of prematurity and association with gender, gestational age and birth weight.*

ROP: Retinopathy of Prematurity.

Of all infants diagnosed with ROP, 26% (34/133) needed treatment, while the rest (74% (99/133)) regressed spontaneously. 100% of infants born less than 750g have been treated. This ratio was 38%; infants with BW 750 - 999g, 36%; infants with BW 1000 - 1249g, 22%; infants with BW 1250 - 1449g, 29%; infants with 1500 - 1749g, 0.05%; infants with 1750 - 1999g, 25%; infants with 2000 - 2449g and 11%; infants with BW ≥ 2500g. 45% of infants born less than 28 weeks have been treated. This ratio was 25%; infants with GA 28 - 31w, 24%; infants with GA 32 - 34w, 1%; infants with GA 35 - 37w.

Discussion

ROP is a preventable blinding disease of the retina. Although diagnosing and treatment methods have been developed, ROP still threat premature infants all over the world especially in middle-income countries such as Turkey, China, Eastern Europa, Latin America, and Asia. Detection and treatment with the screening programs are very important to prevent poor vision. For screening programmes, detection of the risk factors and incidence of ROP are essential. There are several risk factors in the development of ROP but the BW and GA are considered the most important risk factors of the disease [5].

Its incidence differs from country to country. In low and middle income-countries the number of infants with ROP are higher than those in high-income countries. In China, in 2008, the incidence of ROP in infants with BW < 2000g or GA < 34wk was 10.8% [6]. Another study from China in 2013, the incidence of any stage of ROP was 17,8% [7]. In this study Xu., *et al*. found that the incidence of ROP was 55.8% GA ≤ 28wk and 26.8% GA between 29 -3 2 weeks. They also found that the incidence of ROP was 54.5% BW ≤ 1000g and 37.6% BW ≤ 1500g. In this study, 6.8% of preterm infants underwent laser photocoagulation therapy or other treatments. In 2017, Li., *et al.* reported that the incidence of any stage of ROP was 11.9% and 2.0% infants receiving treatment in 2997 preterm infants [8].

In Brazil, Zin., *et al*. found that the incidence of ROP was 16.9% and 3.6% of screened infants needed treatment [9]. From North America, Stoll., *et al.* reported that ROP (any stage) incidence was 59% and severe ROP incidence was 16% in preterm infants with gestational age of 22 to 28 weeks and BWs of 401 to 1500g [10].

In our study, the overall incidence of ROP was 35% and incidence of any stage of ROP was 100% of infants with GA less than or equal to 28 weeks and 63% with GA less than or equal to 32 weeks. We also found that the incidence of ROP BW with < 750g was 100%, 750 - 999g was 91%, 1000 - 1249g was 71% and 1250 - 1499g was 44%. Comparing the incidence of ROP in other middle-income countries, the incidence of the disease was higher in our study. In our study 26% of preterm infants needed treatment, this incidence ratio also higher than other middle-income countries. People who live in our city most of them have low socioeconomic condition and low educational level. We think that the reason for the high incidence rate associated with this situations.

We examined the studies which were reported from high-income countries. In France, the incidence of ROP in infants with GA < 31wk or BW < 1500g was 15% [11]. Two studies from Sweden, Larsson., *et al.* and EXPRESS study showed us the incidence of any stage of ROP in preterm infants with BW < 1500g was 18%, BW < 1000g was 34% and GA < 27wk was 61% [12,13]. Studies from the USA, they found a correlation with gestational age, the incidence of ROP increase from 35% at a gestational age of 31 weeks to 95% at 24 weeks, they also found that the incidence of all stages of ROP, ranging from 40% in infants with a birth weight of 1101 - 1200g to 90% in infants of 501 - 600g [14,15]. Another study from USA, Owen., *et al*. found that the overall ROP incidence proportion in their population was 47.5%, which decreased to 12% for severe ROP [16].

The CRYO-ROP study, the incidence of all stages of ROP was found 65.8% in more than 4000 preterm infants with BWs less than 1251g [17]. The incidence was higher in infants with BWs less than 750 g (90%) than in those weighing between 751 and 1000g (78%) or 1001 to 1250g (47%). From Canada, The overall ROP incidence in their study was 15.6% and severe ROP was documented in 5.2% of infants [18]. They found that the incidence of ROP requiring either operation or anti-VEGF treatment was 9.2% of infants

In Turkey, Bas., *et al.*'s study, which involved 15.745 preterm infants, they reported the incidence of any stage of ROP was 35.6% and 13.3% in infants with GA ≤ 32 weeks and > 32 weeks, respectively, and 42% and 13.4% in those with BW ≤ 1500g and > 1500g, respectively [19]. They found that the overall incidence of ROP in this study was 30%. Another study from Turkey, In 2014, Kavurt., *et al*. reported that the incidence of any stage of ROP was 28.2% and severe ROP was 5.8% in preterm infants ≤ 1500g birth weight or ≤ 32 weeks gestational age [20]. In 2016, Gunay., *et al.* found an incidence 0.61% of severe ROP in infants with BW > 1500g in 5920 preterm infants [21].

In 2018, in TR-ROP study which was a prospective, multicentre study in 69 neonatal intensive care units, the incidence of any stage of ROP was found 27%, severe ROP was found 6.7% in 6115 infants [22]. In this study the incidence of ROP with GA ≤ 28wk was 62.9%, 29 - 32wk was 19.4%, 33 - 35wk was 6.1% and > 35wk was 4.1%, severe ROP incidence was 21.6%, 2.2%, 0.6%, and 0%, respectively. They also found that the incidence of ROP BW with < 1000g was 68%, 1001 - 1250g was 40%, 1251 - 1500g was 20.8%, 1501 - 2000g was 10.3% and > 2000g was 3.8%, severe ROP incidence was 26%, 6.8%, 2.5%, 1% and 0%, respectively.

In compare to the incidence of ROP reported from other studies (in our country), ROP incidence in our study is higher than other studies. In our country, our city is less developed-region and socioeconomic status of the population is low and these situations can explain the reason for high incidence. The other reasons may be low prenatal care, delivery care, and postnatal care standards.

Screening criteria usually base on gestational age and birth weight. Several studies have been done to create criteria for ROP screening programmes. These programmes differ from one country to another country and change from time to time. For example, in the United States(US), first screening criteria was recommended in 1997 and it was revised 2001, 2006 and 2013 [23-25]. The last screening programme suggests that infants with BW of less than or equal to 1500 g or GA of less than or equal to 30 weeks [26]. In the United Kingdom(UK) screening criteria were first developed in 1990 and it was revised in 1995 and 2008 [26,27]. The last criteria state that infants with BW of less than 1251g or GA of fewer than 31 weeks must be screened for ROP and infants with BW of 1251 to less than 1501g or GA of fewer than 32 weeks should also be examined [27].

The US and UK are high-income countries and their screening criteria might not be appropriate for middle-income countries. In China, The Ministry of Health recommended that infants with BW of less than or equal to 2000g and/or GA of less than or equal to 34 weeks must be screened for ROP in 2004. In 2013, Xu., *et al*. suggested that infants with GA less than or equal to 33 weeks and/or BW less than or equal to 1750g must be screened [7].

In our country, there is not a guideline for ROP screening criteria. Bas., *et al.* suggested that ROP screening criteria in Turkey should include a risk factor profile for infants born at < 32 weeks and/or < 1500g BW because in their study, 41 neonates with BW > 1500g underwent laser photocoagulation therapy and the rate of laser treatment in infants born at > 32 weeks' GA was 0.5% (20 infants) [19]. In 2017, In TR-ROP study, screening criteria was stated to be infants with a GA ≤ 34 weeks or a BW < 1700g in Turkey [22]. Based on the result of our study, we recommend that infants with ≤ 1750g or ≤ 35wk should be examined. Infants with BW ≥ 2000g and have any risk factors such as oxygen therapy should also be examined.

This study has some limitations. First of all, the study population is a little small. Second, risk factors except for BW an GA were evaluated. Third, the study was conducted in Adana, so the results may not reflect the true incidence of ROP in Turkey.

Conclusions

ROP is still a serious disease and its incidence is different between countries and change from time to time according to the neonatal healthcare units conditions and their developments. Countries should create their own criteria and revise it at certain intervals. Screening criteria for ROP in Turkey must be wider than high-income countries. In Turkey, neonatal healthcare unit conditions should be improved and national guideline for ROP should be established.

Conflict of Interest

None.

Author Contributions

Selim Cevher: Study conception and design, Acquisition of data, Drafting of the manuscript, Critical revision, Statistical analysis.

Emine Alyamac Sukgen: Acquisition of data, Analysis, and interpretation of data.

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