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Screening results for retinopathy of prematurity: A retrospective study

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Abstract

Aim: The aim of this study was to determine the frequency of ROP development in premature infants hospitalized in the neonatal intensive care unit and/or referred to the ROP Diagnostic Unit of our hospital and to emphasize the importance of cooperation between ophthalmologists and neonatologists in the treatment and follow-up of infants with ROP.

Materials and Methods: The findings of 287 premature infants who were followed and treated in the neonatal intensive care unit between January 2017 and November 2022 and then referred to the ROP Diagnostic Unit were retrospectively analyzed. They were classified according to birth weight and gestational age. They were divided into 4 groups according to birth weight (under 1000 g, between 1000-1250 g, between 1250-1500 g and over 1500 g) and 3 groups according to gestational age (under 28 weeks, between 29-32 weeks and over 33 weeks). ROP development rates were determined in these groups. Those who developed retinopathy of prematurity were classified according to their stages.

Results: A total of 287 premature infants (141 boys and 146 girls) were included in the study. Twenty-eight of the premature babies were Syrian (9.8%). Mean gestational age at birth was 32.34 weeks (min. 24, max. 37) and mean birth weight was 1830.12 g (min. 750 g, max. 4000 g). 34 babies (11.8%) had stage 1 ROP and 12 babies (4.1%) had stage 2 ROP. 14 babies (4.9%) had plus. Due to the rapid progression of the clinic, 20 patients (7%) with stage 2 or higher ROP and plus were referred to an advanced center with ROP treatment center certification.

Conclusion: Premature babies born under 34 weeks of gestation should be examined for retinopathy of prematurity. Early diagnosis of retinopathy of prematurity is very important to prevent blindness due to ROP, even if treatment is not possible according to local conditions.

Introduction

Retinopathy of prematurity (ROP) is a developmental vascular proliferative disorder that occurs in the retina of premature infants before the retinal vasculature is complete. ROP is a major cause of childhood blindness and severe visual impairment. With advances in neonatal intensive care all over the world, ROP in premature infants has become a serious morbidity with increasing frequency due to the decrease in neonatal mortality and increase in the survival rate of micropremature infants. In a single-center retrospective consecutive case series of more than 30 years, it was emphasized that the incidence of ROP tended to decrease over time, while babies with ROP had lower gestational age and birth weight. In the same study, it was shown that especially micropremature infants developed more severe ROP and plus disease and the need for treatment was higher in parallel [1].

The frequency and severity of retinopathy of prematurity vary from country to country and even in intensive care units. The care of patients in intensive care units and the screening protocols applied play an important role in this. In our country, the guidelines prepared jointly by the Turkish Neonatology Association and the Turkish Ophthalmology Association as well as the guidelines published by the American Academy of Pediatrics and the American Association of Pediatric Ophthalmology and Strabismus are accepted for both screening and follow-up and treatment protocols [2].

In addition to prominent risk factors such as prematu-

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rity, low birth weight and oxygen therapy, respiratory distress syndrome, intraventricular hemorrhage, perinatal asphyxia, sepsis and apnea of prematurity are also considered responsible for the development of retinopathy [3,4-7]. The aim of this study was to determine the frequency of ROP development in premature infants hospitalized in the neonatal intensive care unit and/or admitted to the ROP Diagnostic Unit of our hospital and to emphasize the importance of cooperation between ophthalmologists and neonatologists in the treatment and follow-up of infants with ROP.

Materials and Methods

Premature infants who were followed up in the neonatal intensive care unit of our hospital between January 2017 and November 2022 and who had ROP examination and premature infants who were referred to our ROP diagnosis center from external centers were included in the study. Prior to the study, approval was obtained from the Ethics Committee of Malatya Turgut Özal University (Ethics committee no: 2022/206) and patient records were retrospectively reviewed. The study was planned and conducted in accordance with the principles of the Declaration of Helsinki.

Patients with congenital cataract, microphthalmia and glaucoma were not included in the study. Patients were grouped according to both gestational age and birth weight. Three groups were formed as those with a gestational age of 28 weeks or less, between 28-32 weeks and over 32 weeks. According to birth weights, 4 groups were formed as those born under 1000 g, between 1000-1250 g, between 1250-1500 g and over 1500 g and comparisons were made. All premature babies born younger than 34 weeks were examined for retinopathy, including those born younger than 37 weeks when necessary, considering the patient's risk factors.

The first ophthalmologic examination was performed at postnatal week 4. Topical anesthetic drops were instilled after pupil dilatation with 2.5% phenylephrine and 0.5% tropicamide before ROP examinations. Fundus examinations were performed with indirect ophthalmoscope and 28D lens. Indentation was performed especially to see zone 3 and 360 degree retinal examinations including peripheral retina were performed. Retinal findings of the patients were evaluated according to international classification criteria including location, stage and presence of plus disease. Each patient was classified according to the International Retinopathy of Prematurity classification according to the more advanced retinopathy stage [8].

Patients with no ROP findings were followed up at 2-4 week intervals until retinal vascularization was completed. Patients who developed stage 1 ROP but did not have plus disease and did not progress in follow-up examinations were followed up closely at 1-2 week intervals until retinopathy regressed. Patients who required treatment were treated in a center with a ROP treatment center certificate. All patients were followed up ophthalmologically for possible refractive error and strabismus after the end of the follow-up period for ROP.

Statistical analysis

The sample size of this retrospective study was calculated using the G*Power statistical program (ver.3.1.9.7). Accordingly, the minimum sample size was determined as "54 samples/patient" with a power of 0.95, effect size of 0.5 and type-1 error (α) of 0.05.

Numerical data used in the study were summarized by median (95% confidence interval) and interquartile range, while categorical data were summarized by number (percentage). The conformity of the numerical variables to normal distribution on the basis of groups (birth weight (1000 g and under, 1000-1250 g, 1250-1500 g, 1500 g and over), gestational week (28 weeks and under, 29-32 weeks, 33 weeks and over)) was examined by Shapiro-Wilk test. Since the numerical variables in the two groups (birth weight, gestational week) did not meet the normal distribution requirement, the difference between the groups on the basis of variables was analyzed by Kruskal-Wallis test. Conover test was used for pairwise comparisons after Kruskal-Wallis test. IBM SPSS Statistics 26.0 software was used for statistical analysis. $p<0.05$ was considered statistically significant.

Results

A total of 287 premature infants (141 boys and 146 girls) were included in the study. The mean weight of the babies was 1830 g (min. 750 g, max. 4,000 g) and the mean gestational age was 32 weeks (min. 24, max. 37). There was a statistically significant difference between the rates of ROP development in babies with lower birth weight and gestational age compared to birth weight and gestational age ($p<0.001$).

The rate of infants who developed ROP was 16.02%. 34 infants (11.8%) had stage 1 ROP and 12 (4.1%) had stage 2 ROP. In staging according to zones, zone 3 stage 1 ROP was detected in 22 babies (7.7%), zone 3 stage 2 ROP in 2 babies (0.7%), zone 2 stage 1 ROP in 12 babies (4.2%) and zone 2 stage 2 ROP in 10 babies (3.5%). 14 babies (4.9%) had plus. Twenty patients (7%) were referred to a center with a ROP treatment center certificate due to the presence of stage 2 or higher ROP and plus. Since infants with stage 2 ROP were referred, our clinic does not have a record of infants with stage 3 or higher ROP. Infants who were followed up again after laser photocoagulation and intravitreal anti-VEGF treatment did not develop stage 3 or higher ROP.

Tweenty-eight (9.75%) premature infants were Syrian. ROP development was observed in 6 (21.4%) Syrian babies.

Tweenty babies (6.9%) were referred to a center with ROP treatment center certificate for follow-up and treatment due to the presence of Stage 2 ROP and Plus.

Table 1 and Table 2 show the demographic data of the patients according to birth weight and gestational week. It was observed that babies with a lower birth week and birth weight developed ROP statistically more frequently ($p<0.001$) and therefore the referral rate was statistically higher in that group.

Table 3 shows the rates of ROP development according to birth week. Statistically higher rates of ROP were observed in babies with a lower birth week. 75% ($p<0.001$),

Table 1. Birth weights and demographic data of premature infants.

		Birth weights								p-value
		1,000 g and under (n=7)		1,000-1,250 g (n=28)		1,250-1,500 g (n=51)		1,500 g and over (n=201)		
		Count	Percent %	Count	Percent %	Count	Percent %	Count	Percent %	
Gender	Male	2	28.6%	16	57.1%	26	51.0%	97	48.3%	0.565*
	Female	5	71.4%	12	42.9%	25	49.0%	104	51.7%	
Referred	No	2	28.6%	20	71.4%	46	90.2%	199	99.0%	**<0.001***
	Yes	5	71.4%	8	28.6%	5	9.8%	2	1.0%	
Syrian	No	6	85.7%	23	82.1%	43	84.3%	187	93.0%	0.108*
	Yes	1	14.3%	5	17.9%	8	15.7%	14	7.0%	
ROP(+)	No	0	0.0%	13	46.43%	39	76.5%	189	94.1%	**<0.001***
	Yes	7	100%	15	53.57%	12	23.5%	12	5.9%	

*: Pearson Chi-Square test.

Table 2. Gestational weeks and demographic data of premature infants.

		Gestational week						p-value
		28 weeks and under (n=28)		29-32 weeks (n=94)		33 weeks and over (n=165)		
		Count	Percent %	Count	Percent %	Count	Percent %	
Gender	Male	15	53.6%	49	52.1%	77	46.7%	0.619*
	Female	13	46.4%	45	47.9%	88	53.3%	
Referred	No	17	60.7%	85	90.4%	165	100.0%	**<0.001***
	Yes	11	39.3%	9	9.6%	0	0.0%	
Syrian	No	22	78.6%	82	87.2%	155	93.9%	**0.02***
	Yes	6	21.4%	12	12.8%	10	6.1%	
ROP(+)	No	7	25%	72	76.6%	162	98.2%	**<0.001***
	Yes	21	75%	22	23.4%	3	1.8%	

*: Pearson Chi-Square test.

Table 3. ROP development rates according to birth weight.

		Birth weights								p-value
		1,000 g and under (n=7)		1,000-1,250 g (n=28)		1,250-1,500 g (n=51)		1,500 g and over (n=201)		
		Count	Percent %	Count	Percent %	Count	Percent %	Count	Percent %	
Zone 3 Stage 1 ROP	No	7	100.0%	21	75.0%	44	86.3%	193	96.0%	**<0.001***
	Yes	0	0.0%	7	25.0%	7	13.7%	8	4.0%	
Zone 3 Stage 2 ROP	No	7	100.0%	27	96.4%	50	98.0%	201	100.0%	0.113*
	Yes	0	0.0%	1	3.6%	1	2.0%	0	0.0%	
Zone 2 Stage 1 ROP	No	3	42.9%	22	78.6%	50	98.0%	200	99.5%	**<0.001***
	Yes	4	57.1%	6	21.4%	1	2.0%	1	.5%	
Zone 2 Stage 2 ROP	No	4	57.1%	27	96.4%	48	94.1%	198	98.5%	**<0.001***
	Yes	3	42.9%	1	3.6%	3	5.9%	3	1.5%	
		Median (95%CI)	IQR	Median (95%CI)	IQR	Median (95%CI)	IQR	Median (95%CI)	IQR	
Gestational week		27(24-29)	3	29(28-30)	2.75	30(29-31)	3	34(33-34)	1	**0.001****

*: Pearson Chi-Square test, **: Kruskall-Wallis Test, CI: Confidence Interval, IQR: Interquartile range.

Table 4. ROP development rates according to gestational week.

		Gestational week						p-value
		28 weeks and under		29-32 weeks		33 weeks and over		
		Count	Percent %	Count	Percent %	Count	Percent %	
Zone 3 Stage 1 ROP	No	20	71.4%	82	87.2%	163	98.8%	**<0.001***
	Yes	8	28.6%	12	12.8%	2	1.2%	
Zone 3 Stage 2 ROP	No	27	96.4%	93	98.9%	165	100.0%	0.096*
	Yes	1	3.6%	1	1.1%	0	0.0%	
Zone 2 Stage 1 ROP	No	22	71.4%	88	93.6%	165	100.0%	**<0.001***
	Yes	6	28.6%	6	6.4%	0	0.0%	
Zone 2 Stage 2 ROP	No	22	71.4%	91	96.8%	164	99.4%	**<0.001***
	Yes	6	28.6%	3	3.2%	1	.6%	
		Median (95%CI)	IQR	Median (95%CI)	IQR	Median (95%CI)	IQR	
Birtweight		1235 (1100-1300)	305	1500 (1455-1575)	395	2020 (1960-2100)	517.5	**<0.001****

*: Pearson Chi-Square test, **: Kruskall-Wallis Test, CI: Confidence Interval, IQR: Interquartile range.

23.4% (p<0.001), and 1.8% (p<0.001) of the babies born at 28 weeks and below, 29-32 weeks, and 33 weeks and above, respectively, developed ROP.

Table 4 shows the rates of ROP development according to birth weight. A statistically significant difference was observed in the rates of ROP development in babies with lower birth weight and week of gestation compared to birth weight and week, except for Zone 3 Stage 2 ROP (p<0.001).It was also observed that ROP developed in all babies (100%) under 1,000 g. It was observed that 53.57% of babies born between 1,000-1,250 g, 23.5% of babies born between 1,250-1,500 g, and 5.9% of babies born over 1500 g developed ROP. It was also observed that the presence of Plus was statistically higher in babies with low birth weight (p<0.001).

Discussion

In this study, the rate of infants with ROP was 16.02%. 11.8% had stage 1 ROP and 4.1% had stage 2 ROP. Due to the rapid progression of the clinic, 20 patients (7%) were referred to an advanced center with a ROP treatment center certificate due to stage 2 and above ROP and plus disease. The proportion of infants who developed ROP and were referred for treatment was 43.4% of all infants with ROP. ROP development rates were found to be higher in babies with lower birth weights and weeks of gestational age compared to birth weight and weeks of gestational age, except for Zone 3 Stage 2 ROP.

Determining the incidence of retinopathy of prematurity is difficult due to various reasons such as differences in gestational ages and differences in neonatal intensive care facilities in hospitals. In a multicenter study (ET-ROP), the incidence of ROP was found to be 68% in all newborns with a birth weight of less than 1251 g [9]. The rate of premature infants below 1250 g requiring treatment was reported to be 5% [10,11].

In studies conducted in our country, the prevalence of ROP varies between 10% and 36.3% [12-19]. In the study by Kavuncuoğlu et al. found stage 1 in 50%, stage 2 in 36.7%, stage 3 in 10% and stage 4 in only 1 case (1.3%) [18]. Öner et al, stage 1 was found to be 76.5%, stage 2 20.3%, and stages 4-5 3.2% [19]. In studies conducted in Turkey, the mean gestational age of cases with ROP was reported to be 27-32 weeks and the mean birth weight was reported to be between 1,122-1,568 g [12-20]. In our study, the rate of ROP was similar to other studies conducted in Turkey.

Many risk factors have been defined for retinopathy of prematurity. Some of these risk factors are contradictory and some are rare, so generalization could not be made. It has not been fully clarified because they are confused with other risk factors. There are various reasons for these. Heterogeneity due to differences in origin, race, and differences in basic characteristics of infants such as gestational age and weight may affect clinical outcomes. Syrian babies in our region were also included in our study in terms of the evaluation of origin and race differences. 6 (21.4%) of 28 (9.75%) Syrian premature infants developed ROP. 'We think that the incidence of ROP in Syrian premature infants (21.4%) may not be higher than that in Turkish infants (15.4%) because Syrians do not usually bring their premature infants to ROP controls and there is a large difference between the numbers of Turkish and Syrian premature infants for comparison'.

Differences in neonatal intensive care study protocols in hospitals in different countries cause differences in ROP results due to prematurity morbidity. Another reason is that clinical experience among ophthalmologists causes differ-

ences in ROP studies. Disagreements among ophthalmologists about the need for diagnosis and treatment may affect the results of ROP studies [21-23].

The Vermant Oxford Network database, which collects data from more than 1000 NICUs worldwide, estimates the incidence of ROP as 33.2% in newborns under 3,500 g in 2010 [24]. The incidence rates of ROP development vary from country to country due to differences in neonatal intensive care protocols and mortality rates and differences in the population included in the study. Many studies have shown that babies who develop ROP in low- and middle-income countries have a higher mean gestational age and birth weight than babies who develop ROP in the USA [25].

In high-income countries, the incidence of ROP in infants weighing less than 1,500 g is reported to be 60%. In middle-income countries, the incidence of ROP varies significantly in babies with a larger birth week and higher birth weight compared to high-income countries due to birth conditions, survival rates, and changing standards of neonatal intensive care [26]. In our study, it was observed that ROP developed with a rate of 100% in babies born below 1,000 g, 53.57% in babies born between 1,000-1,250 g, 23.5% in babies born between 1,250-1,500 g, and 5.9% in babies born above 1,500 g.

Akman et al. emphasized that ROP screening programs should be evaluated according to local conditions in their study in which screening criteria in Turkey were re-evaluated. According to this study, it is recommended to screen those who are younger than 34 weeks and have a birth weight below 1850 g in our country [27]. In this retrospective study conducted in a province in the Eastern Anatolia region, premature babies younger than 37 weeks were evaluated. The babies born between 34-37 weeks and included in the evaluation were hospitalized in the neonatal intensive care unit and required oxygen therapy. Babies older than 34 weeks did not have retinopathy in our study. ROP developed in 3 (1%) of the babies born between 32-34 weeks. When compared to all babies with ROP, it was observed with a rate of 6.5%.

Our incidence of retinopathy of prematurity is 16.02% due to the effect of our neonatal intensive care protocol and the lower number of infants with low gestational age and birth weight at birth. Risk factors for the development of retinopathy of prematurity were not evaluated in our study, but our examinations are performed more frequently in infants with known risk factors. Knowing the risks for retinopathy of prematurity helps to determine the screening criteria and to determine the examination intervals according to the risk status of the premature infant. It also allows us to reduce the number of unnecessary examinations by reducing the frequency of examinations in premature babies who do not have risk factors and are less likely to develop ROP.

Conclusion

In conclusion, we believe that the detection of retinopathy of prematurity, which may threaten vision, with screening even in regions where treatment facilities are limited and referring babies to advanced centers is very valuable in order to shed light on the future of these babies.

Disclosure

Authors declared no financial support.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

Approval for the study was obtained from the Malatya Turgut Özal Univercity Clinical Research Ethics Committee dated 2022/206.

Authors' contributions

The study was planned by Z.E.G. and N.A.M. The experiments were done by Ş.Y. and Z.E.G. contributed to the collection, analysis, and interpretation of the data. N.A.M. drafted the article and revised it. Z.E.G. gave final approval of the version to be published. All authors reviewed the manuscript.

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