

# Refractive Status of Premature Babies with or without Retinopathy of Prematurity at the Age of 1–5

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## ABSTRACT

**Objective:** In children, refractive status is affected by a lot of factors such as congenital disorders, prematurity, and retinopathy of prematurity (ROP). Our study aimed to evaluate the effect of ROP development on visual acuity, strabismus, and refractive errors in children born premature.

**Methods:** The study included 60 eyes of 30 premature infants born <36 weeks. The infants were divided into two groups as; which developed ROP (Group I) and group which undeveloped ROP (Group II). First year refractive status, refractive status on the control examination of the fifth age, visual acuity, strabismic examination findings, anterior, and posterior segment findings were recorded. Two groups were statistically compared in terms of refraction status of both first and fifth age and visual acuity of fifth age.

**Results:** There were 16 (53.3%) male and 14 (46.67%) female premature infants born before 36 weeks. Group I developed of ROP comprised of 22 eyes and Group II comprised of 38 eyes with no ROP. A statistically significant difference was found between the rates of myopia at the age of 1 and 5 years. The incidence of myopia was found statistically high in both ages ( $p=0.0001$  and  $p=0.006$ , respectively) in Group I patients. There was no statistically significant difference in both first age and fifth age examination findings in terms of hypermetropia and astigmatism ( $p=0.475$  and  $p=0.694$ , respectively,  $p=0.103$  and  $p=0.81$ , respectively). There was no significant difference between the two groups in terms of mean visual acuity values measured at the age of 5 ( $p=0.054$ ).

**Conclusion:** It was concluded that prematurity alone did not lead to an increase in the incidence of myopia, but there was a significant relationship between the development of the ROP and myopia incidence. Infants with ROP should be closely followed in subsequent years.

## INTRODUCTION

Prematurity, regardless of retinopathy of prematurity (ROP), carries an increased risk of ocular morbidity for lifetime.<sup>[1]</sup> Although the visual acuity and contrast sensitivity of pre-term infants were measured in the normal range when measured in the later stages of life, the mean values were significantly lower than the term.<sup>[1,2]</sup> The most common of the other eye problems that may occur even if the ROP does not develop are strabismus, high refractive errors (especially myopia), and visual impairment related to visual path damage.<sup>[3]</sup>

The late embryonic phase in the intrauterine life and the early phase after delivery is critical in the maturation of the eye, especially in the refractive development. In premature babies, especially in patients with ROP, the mat-

uration and emmetropization of the eye are affected due to immaturity.<sup>[4,5]</sup> Myopia, astigmatism, anisometropia, and strabismus are more frequently encountered in premature babies regardless of ROP status whereas babies born in term are generally hypermetropic.<sup>[6-10]</sup>

We aimed to investigate the refractive status of premature babies with or without ROP, visual acuity, and strabismus status at the age of 1–5 in our study.

## MATERIALS AND METHODS

The medical records and ROP files which obtained from The Ophthalmology Clinic of Kartal Dr. Lutfi Kırdar Training and Research Hospital infants born between March 2010 and June 2011 were retrospectively reviewed. Pre-

mature infants born before the 36<sup>th</sup> gestational week and/or below 1500 g and babies with risk required consultation according to the neonatal specialists were enrolled the study. Babies not come to first and fifth age control visit and ones with growth retardation, central nervous system disease, or syndromic likely to be effect on visual acuity were excluded from the study. The study was in accordance with the principles of the Declaration of Helsinki and the approval of the Local Ethics Committee was obtained. Sixty eyes of 30 babies born before 36 weeks were included in the study. The infants were divided into two groups as premature infants who developed ROP and not developed the ROP. The gender of the infants, birth week, birth weight, development of ROP, 1st year refractive status, fifth age refractive status, visual acuity, strabismus examinations, anterior segment, and posterior segment findings were recorded. When optic disc cupping detected intraocular pressures of the infants were measured by Tono-Pen (Tono-Pen AVIA applanation tonometer, Reichert, USA) and followed up for glaucoma.

### Retinopathy of Prematurity Scanning

The first examination time of the patients was determined according to the criteria of American Academy of Pediatrics, American Association for Pediatric Ophthalmology and Strabismus, and American Academy of Ophthalmology. According to the results of the examination, follow-up and appropriate treatments were recommended to the patients at appropriate intervals or after the maturation was determined, ROP follow-up was terminated.<sup>[11,12]</sup> Patients were divided in to two groups according to the first scanning examination findings as those developed stage 1-2-3 ROP and had no ROP.

### Refractive Status Assessment

The first age refraction measurements were measured with non-cycloplegic automatic infrared videoretinoscopy (PlusoptiX S08). Cycloplegic retinoscopy was performed in children who could not be measured with PlusoptiX S08 or whose spherical and cylindrical values were above 1 dioptrics (D) or anisometropia over 1D. On examination of the fifth age refraction, Cyclopentolat (%1 Sikloplejin, Abdi İbrahim, Turkey) was applied two times in five minutes interval in both eyes of all children. One hour after the drop, the measurement was performed with the classical autorefractometer (Topcon RM A7000B) and confirmed by retinoscopy (Welch Allyn retinoscope). Spherical equivalence (SE) values of the obtained refraction measurements were recorded. While the values of SE -0.50 and below were evaluated as myopia, SE +2.00 D and above as hypermetropia, cylindrical values of 1.00 D and above were recorded as astigmatism. In case the difference in refraction between the eyes more than 1D status was defined as anisometropia.

### Measurement of Visual Acuity

Snellen E match was used for visual acuity measurement and the obtained values were recorded as logMAR. The

right and left eyes were measured separately.

### Strabismus Examination

The presence of strabismus was evaluated by Hirschberg and cover test. Versions and ductions were recorded according to the results eye movements examination.

### Statistical Analysis

SPSS 16.0 (Statistical Package for the Social Sciences) was used for statistical analysis of the results. Descriptive statistics (mean, standard deviation, and frequency) were used to analyze the data of the study. The Mann-Whitney U test was used to compare the two groups of non-normally distributed measurement variables and Wilcoxon Signed Ranks test was used to compare the measurement variables. The t test was used in comparison of the measurement variables in normal distribution and paired t-test was used in comparison of the each other of the measurement variables. Frequency analysis was performed by Pearson Chi-square test.

## RESULTS

The study included total 60 eyes of 30 (16 male and 14 female) infants born before 36 weeks of age. Patients were grouped according to the development of ROP in first examination as Group 1, comprised up 22 eye of 11 infants with ROP (36.6%) and Group 2, comprised up 38 eye of 19 infants without ROP (Table 1). Stage 3 ROP developed in 6 (27.2%), Stage 2 ROP developed in 7 (31.8%), and Stage 1 ROP developed in 9 (40.9%) of the Group 1 eyes. Laser photocoagulation was performed in four eyes of two babies in group with ROP developed. None of the patients had Stage 4 or higher ROP during follow-up period. In addition two of the 30 premature babies with ROP, only one eye had involved disease while the other eye had not.

The mean gestational age of the first group developing ROP was  $30 \pm 2.69$  (range=25–33) weeks, the mean birth weight was  $1.541 \pm 577.8$  (range=695–2750) grams, and the mean age at the final visit was  $58.45 \pm 4.41$  (range=52–66) weeks. The mean gestational age in Group 2 without ROP was  $33.26 \pm 2.12$  (range=28–36) weeks, mean birth weight was  $2.136 \pm 510.05$  (range: 1240–3410) g, and the mean age at the final visit was  $61.05 \pm 4.59$  (range 51–66) months. The gestational age and birth weight were significantly lower in the group with ROP group compared with the group without ROP ( $p < 0.01$ ) (Table 2).

**Table 1.** The distribution of the patients according to the development of retinopathy of prematurity

Group	Frequency (%)
ROP (+)	22 (36.67)
ROP (-)	38 (63.33)
Total	60 (100)

ROP: Retinopathy of prematurity.

**Table 2.** Mean values according to groups

Groups	Mean±SD		p-value
	ROP (+) (n=22)	ROP (-) (n=38)	
Gestational week	30.00±2.69	33.26±2.13	0.0001 <sup>a,*</sup>
Birth weight (g)	154,182±57,783	2.136±51,005	0.0001 <sup>a,*</sup>
Last control age (month)	58.45±4.41	61.05±4.59	0.071 <sup>a</sup>
ROP stage	1.86±0.83	-	
1 age spherical value (D)	0.85±1.26	1.29±0.62	0.135 <sup>b</sup>
1 age cylindrical value (D)	-0.90±0.59	-0.92±0.57	0.939 <sup>b</sup>
Axle angle (1 age)	94.13±76.61	71.68±63.04	0.225 <sup>a</sup>
1 age spherical equivalent (D)	0.33±1.49	0.82±0.54	0.070 <sup>b</sup>
5 age spherical value (D)	1.17±1.49	1.37±0.75	0.484 <sup>a</sup>
5 yaş cylindrical value (D)	-1.09±0.88	-0.64±0.50	0.015 <sup>b,*</sup>
Axle angle 5 age	75.68±68.76	67.84±41.0	0.630 <sup>b</sup>
5 age spherical equivalent (D)	0.62±1.73	1.09±0.70	0.234 <sup>b</sup>
Visual acuity (logMAR)	0.11±0.13	0.04±0.05	0.054 <sup>a</sup>

<sup>a</sup>p<0.05, <sup>a</sup>Mann-Whitney U-test, <sup>b</sup>t-test; SD: Standard deviation; ROP: Retinopathy of prematurity; logMAR: Logarithm of the minimum angle of resolution.

As the evaluation of the distribution of refraction in Group 1, at first age emmetropia was observed in 8 (36.3%) eyes, myopia (mean-1.25D) in 7 (31.8%) eyes, astigmatism (mean 1.38 D) in 11 eyes, and hypermetropia (mean+2.71D) in three eyes. In the 5th year controls; 6 eyes (27.2%) were emmetropic, 7 eyes (31.8%) had myopia (mean-1.31D), 10 eyes (45.4%) had astigmatism (mean 1.92D), and 5 eyes (22.7%), hypermetropia (mean+2.77 D) was present.

A statistically significant difference was found between the first age spherical equivalent mean and the fifth age spherical equivalent mean of both groups. First age values were significantly lower (p=0.006) (Table 3).

When the refraction distributions of Group 2 (n=38) were examined; while 20 eyes (52.6%) were emmetropic on first age examinations, no myopia was found in any eye. Seventeen eyes (44.7%) had astigmatism (mean 1.44D), and 3 eyes (7.8%) had hyperopia (mean+2.08D). In the 5th year controls; While 25 eyes (65.7%) were emmetropic, in 2 eyes (5.2%) myopia (mean-0.56D), in 9 eyes (23.6%) astigmatism (mean 1.30D) and in 3 eyes (7.8%) hypermetropia (mean+2.62 D) was observed.

In comparison of the Groups 1 and 2, there were consid-

erable differences in terms of the presence of myopia in both first age and fifth age examinations. The incidence of myopia was significantly higher in Group 1 at both ages (p=0.0001 and p=0.006, respectively).

Although there was no statistically significant difference between the two groups in terms of the mean value of visual acuity at 5 years of age, vision was found to be lower in the group with ROP (0.11 logMAR) than in the group without ROP (0.04 logMAR) (p=0.054).

Anisometropia was present in 5 children (16.6%) in the first age examinations of 30 children included in our study, while anisometropia was present in only one child (3.3%) in the 5th age examinations. While anisometropia was 21% (4/19) found on the first age examination in Group 1, it decreased to 5.2% (1/19) at the age of 5 years. There was 9% (1/11) anisometropia on the first age Group 2 and no anisometropia on the fifth age examination. In addition, anisometropia was not observed in two children with ROP involved in one eye. The difference between the anisometropia incidence of the two groups was statistically significant (p<0.01). The incidence of anisometropia is significantly higher in group with ROP. No strabismus was

**Table 2.** Comparison of the refraction values of first and fifth age in all study participants

	Mean±SD		p-value
	First age	Fifth age	
Spheric value	1.13±0.92	1.30±1.07	0.10 <sup>b</sup>
Cylindrical value	-0.91±0.57	-0.80±0.69	0.18 <sup>a</sup>
Axle angle	79.91±68.56	70.71±52.45	0.39 <sup>a</sup>
Spheric equivalent	0.64±1.02	0.92±1.19	0.006 <sup>b,*</sup>

\*p<0.05; <sup>a</sup>Wilcoxon signed ranks test; <sup>b</sup>Paired t-test; SD: Standard deviation.

observed in any of the patients at the fifth age controls.

While the anterior segment examinations of all children in Group 1 and Group 2 at the age of 5 were evaluated normal. There was laser photocoagulation spots in four eyes on the posterior segment examination of the Group 1.

Again in the group with ROP, 4 eyes (18.18%) had increased folding in the retinal vessels and 4 eyes (18.18%) had cupping in the optic nerve. Intraocular pressures (mean  $15.5 \pm 2.06$  mmHg) of 4 eyes with cupping at the optic nerve were within normal limits and the patients were followed up for glaucoma. When the posterior segment findings of the Group 2 were examined; in 2 eyes (5.26%), increased folding in the retinal vessels in 2 (5.6%) eyes, vitreous degeneration in 2 eyes (5.26%), and cupping in the optic nerve were detected in 8 eyes (21.05%).

The intraocular pressure (mean  $13.75 \pm 2.72$  mmHg) was normal in the eyes with cupping, and these patients were followed up for glaucoma.

## DISCUSSION

In prematurity, the high incidence of myopia is attributed to factors such as the increase in corneal curvature, lens sphericity, and flat anterior chamber by some researchers.<sup>[7,13]</sup> According to Fletcher and Brandon, the causes of more frequency of myopia in prematures are faster development of globe leading to changes in lens and corneal curvature.<sup>[14]</sup> In the study of Quinn et al., it was reported that the incidence of myopia was the maximum (21.2%) at the age of 1 in premature infants with ROP and minimum at the age of four and a half (15.7%).<sup>[15]</sup> In another study by Al Oum et al., the rate of myopia was 40.6% in the first age of patients with ROP and this rate decreased to 28% in the 6th year.<sup>[16]</sup>

In our study, the incidence of 1st-year myopia of babies with ROP was 31.8% and was similar to the findings of Al Oum et al.<sup>[16]</sup> This rate was found considerably high compared with the rate (25%) of the Fledelius et al. (study comprised up the children aged 10 years), and rate (26.7%) of Quin et al. (study comprised up children aged 4.5 years with ROP).<sup>[5,7]</sup> We also found that the mean spherical equivalent averages (0.33 D) of the group developing ROP were lower than the spherical equivalent averages (0.62 D) at the age of 5 years. However, this difference was not significant for myopia. Decrease in the incidence of myopia, while the spherical equivalent values increased, can be explained by we classified the values above  $-0.50$  D as myopia. The rate of myopia in the 6th month was found as 2.9% in the study of Holmström and the incidence of first generation myopia was found as 6.9% in infants without ROP in the study of Al Qum et al.<sup>[16]</sup> In our study, there was no myopia at the first age of the infants who did not develop ROP, while the incidence of myopia at the age of 5 years was found to be 5.2% and similar in the study (age 6, 7.4%) of Al Oum et al.<sup>[16]</sup> The fact that we have no any myopia in infants without ROP could be explained by including only babies born 36 weeks and below. Holmström

et al. reported that the incidence of astigmatism was significantly decreased in children born with premature birth from the 6th to the 30th month irrespective of the state of PR development.<sup>[6]</sup> Similarly, Al Oum et al.<sup>[16]</sup> showed a significant decrease in the incidence of astigmatism from age 1 to age 6. We found the incidence of astigmatism for first age and fifth age decreased in both groups with ROP (from 50% to 45.4%) and group without ROP (from 44.7% to 23.6%). However, these differences have not been found statistically significant ( $p > 0.05$ ).

In our study, the 5-year-old astigmatism incidence in the group with ROP (45.4%) was similar to the results of Davitt et al. (42%) and Al Oum et al. (40.9%).<sup>[8,16]</sup> The 5-year-old astigmatism rate of group without ROP was found to be close to that of the previous studies with 23.6% (22%–28.8%, respectively).<sup>[6,17]</sup> Absence of significant decrease in astigmatism at 5<sup>th</sup> year may be due to insufficient number of our patients.

Özdemir et al.<sup>[18]</sup> reported that the incidence of hyperopia was 21% in premature children aged 5-7 years who did not develop ROP. Küçükevcilioğlu et al.<sup>[19]</sup> reported that the incidence of hyperopia was found to be 28.8% in infants who developed intermediate-level ROP, and 22.3% in infants without ROP. In our study, the incidence of hyperopia in children who developed ROP at 5 years of age was similar to other studies with 22.7%, while the rate of children without ROP was found to be lower with 7.8% compared to other studies. As concordance with the other studies, there was no significant difference between the groups with ROP and groups without ROP in terms of the incidence of hyperopia.<sup>[20-22]</sup> The lower incidence of hyperopia in children who not developed ROP may be due to the excluding the babies born nearly in term (birth week until 36 weeks). Tuppurainen et al. found the incidence of hyperopia as 14.3% on the fifth age examination of the infants born in term.<sup>[23]</sup> This finding is concordance with our findings and supports our thesis. However, the studies of Özdemir et al. and Küçükevcilioğlu et al. comprised up infants born 34 weeks and below.<sup>[18,19]</sup> Although cause of the incidence of increased strabismus in premature infants is not clear, it is thought to be due to ROP, increase in refractive defect, anisometropia, low birth weight, and neurological development defect.<sup>[24,25]</sup> Shah et al. reported that the decrease in occipital brain volume in premature infants may cause strabismus.<sup>[26]</sup> Schaliş-Delfos et al. found that the incidence of strabismus increased as gestation age decreased.<sup>[27]</sup> In the study performed by Holmström et al., the incidence of strabismus was found as 40% in infants underwent cryotherapy, whereas it was found as 34% in children with ROP who developed neurological complications, this rate decreased to 5.9% in children without ROP in the absence of neurological problems.<sup>[28]</sup> However, in our study, we have no strabismus in any of the children. This result may be due to excluding the infants with neurological deficiency and/or syndromic from the study. Larsson and Holmström found the incidence of anisometropia in children without ROP at 10 years of age

was 4.2% and 13.7% in children with ROP.<sup>[17]</sup> In a study by Al Oum et al. including 217 premature children, the rate of anisometropia was reported to be 1.6%.<sup>[16]</sup> In our study, While the incidence of anisometropia was 16.6% at the age of 1 year, later decreased to 3.3% at the age of 5 years. In both age groups, the incidence of anisometropia was higher (21% and 5.2%) than in children without PR. The reason for this is that the ROP is mostly symmetrical and the pathologies are similar.<sup>[29,30]</sup>

Many studies reported that there was a decreased visual acuity in the babies born premature regardless of the presence of ROP compared with the babies born in term.<sup>[5,31,32]</sup> In the study conducted by Ozdemir et al., best corrected visual acuity of fifth age was found in normal limits in babies born premature but without ROP and concluded that prematurity not lead to reactive defect at the level which may affect the vision.<sup>[18]</sup> There was no significant difference between the children with ROP and children without ROP in terms of visual acuity in the study conducted by Kucukciliglu et al.<sup>[19]</sup> There was no significant difference among the babies underwent ROP therapy, babies with ROP regressed spontaneously and babies without ROP in terms of visual acuity in the study by Bonotto et al.<sup>[33]</sup> However, there was no significant difference between two groups in terms of fifth age visual acuity in our study, decreased visual acuity has been found in groups with ROP compared with the groups without ROP (0.11 logMAR and 0.04 logMAR, respectively).

Myopia incidence is significantly affected by the factors such as gestational week and birth weight in babies born premature. It could not be reached a conclusive concept about the effect of the development ROP on the incidence of myopia due to the differences in gestational weeks and birth weights of the groups. To understand the effect of ROP on myopia in the future studies, the extension of the study with the proper patient population (have variables close to each other) will enable us to get more detailed information. In addition, to be able to reveal the effect of prematurity on visual acuity more clearly, it will be appropriate to carry out studies by forming a control group with term babies.

It was concluded from our study that prematurity alone did not lead to an increase in myopia incidence and there was a significant relationship between ROP development and the incidence of myopia and astigmatism. We also believe that babies with ROP should be closely followed up in the next years. Our study showed that there was no significant correlation between the development of ROP and visual acuity, strabismus, and anisometropia. Further investigations are need to clearly identify this correlation.

#### Ethics Committee Approval

This study approved by the Kartal Dr. Lutfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 27.04.2016, Decision No: 2016/514/83/3).

#### Informed Consent

Retrospective study.

#### Peer-review

Externally peer-reviewed.

#### Authorship Contributions

Concept: K.B., A.Y.O., M.N.B., Ü.Ç., A.A.; Design: K.B., M.N.B., A.Y.O.; Supervision: K.B., A.Y.O., M.N.B., A.A.; Fundings: K.B., A.Y.O., M.N.B.; Materials: K.B., A.Y.O., M.N.B., Ü.Ç.; Data: K.B., A.Y.O., M.N.B., Ü.Ç.; Analysis: K.B., A.Y.O., M.N.B., Ü.Ç., A.A.; Literature search: K.B., A.Y.O., M.N.B.; Writing: K.B., A.Y.O., M.N.B., Ü.Ç., A.A.; Critical revision: K.B., A.Y.O., M.N.B., Ü.Ç., A.A.

#### Conflict of Interest

None declared.

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## Prematüre Doğan Çocukların 1. ve 5. Yaşlarındaki Refraksiyon Durumları

**Amaç:** Prematüre doğan bebeklerin prematüre retinopatisi gelişimine bağlı olarak 1. ve 5. yaş refraksiyon ölçümleri ile, 5. yaş kontrol muayenelerindeki görme keskinliği ölçümleri ve şaşılık gelişimine olan etkisinin değerlendirilmesi amaçlandı.

**Gereç ve Yöntem:** Çalışmaya 36 haftadan küçük doğan 30 prematüre bebeğin 60 gözü dahil edildi. Bebekler takipleri sırasında prematüre retinopatisi (PR) gelişen (grup 1) ve gelişmeyen (grup 2) prematüre bebekler olmak üzere iki gruba ayrıldı. Bebeklerin cinsiyeti, doğum haftası, doğum kilosunu, PR gelişimi, 1. yaş refraktif durumları ile 5. yaş kontrol muayenesindeki refraktif durumları ile görme keskinlikleri, şaşılık muayeneleri, ön ve arka segment bulguları kaydedildi. PR gelişen grupta PR gelişmeyen grup hem 1. yaş hem de 5. yaşta refraksiyon durumları ile 5 yaşta görme keskinlikleri açısından istatistiksel olarak karşılaştırıldı.

**Bulgular:** Çalışmaya 16'sı (%53.33) erkek ve 14'ü (%46.67) kız olmak üzere 36 haftadan küçük doğan 30 prematüre bebeğin 60 gözünden PR gelişen 22 göz (grup 1) ile PR gelişmeyen 38 göz (grup 2) istatistiksel olarak karşılaştırıldığında, hem 1. yaş hem de 5. yaşta miyopi görülme oranları arasında ileri düzeyde anlamlı bir farklılık bulundu. Grup 1'de (n=22) her iki yaşta da miyopi insidansı daha yüksekti (sırasıyla p=0.0001 ve p=0.006). Hipermetropi ve astigmatizma görülme oranları açısından ise hem 1. yaşta hem de 5. yaşta istatistiksel olarak anlamlı bir farklılık bulunamadı (sırasıyla 1.yaş p=0.475 ve p=0.694 ile 5. yaş p=0.103 ve p=0.81). Beş yaşında ölçülen görme keskinliği değer ortalamaları açısından 2 grup arasında anlamlı bir farklılık yoktu (p=0.054).

**Sonuç:** Tek başına prematüritenin miyopi insidansında artışa yol açmadığı fakat PR gelişimiyle miyopi insidansı arasında anlamlı bir ilişki olduğu, dolayısıyla PR gelişen bebeklerin sonraki yıllarda daha yakından takibinin uygun olacağı kanaatine varıldı.

**Anahtar Sözcükler:** Prematürite; miyopi; prematüre retinopatisi; refraksiyon.