Strabismus in Retinopathy of Prematurity: Risk Factors and the Effect of Macular Ectopia

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Abstract

Purpose

This study aimed to examine factors associated with strabismus in patients with retinopathy of prematurity (ROP) and the relationship between strabismus and macular ectopia.

Methods

Patients with ROP were divided into three groups: Group 1, patients with spontaneous regression (n=45); Group 2, patients who received laser treatment (n=70); and Group 3, patients who underwent surgical treatment (n=91). Rates of anisometropia, amblyopia, nystagmus, macular ectopia, and retinal pathologies were evaluated and their impacts on strabismus development were determined. Disc-to-fovea distance (DFD) was measured from coloured fundus pictures and the correlation of macular ectopia with severity of strabismus was evaluated.

Results

A total of 206 patients were included. Rates of anisometropia, amblyopia, nystagmus, macular ectopia, retinal pathologies causing blindness, and strabismus were higher in Group 3 (p=0.0001) and correlated with higher stages of ROP (p=0.0001). Macular ectopia (p=0.005), retinal pathologies (p=0.005), and amblyopia (p=0.012) had the strongest impact on strabismus development in ROP patients. DFD and severity of strabismus were not significantly correlated (p=0.364). Mean visual acuity (VA) was significantly higher in orthophoric patients compared to those with esotropia and exotropia (p=0.027). Patients with esotropia had lower VA compared to patients with exotropia, but this finding was not statistically significant (p=0.729).

Conclusion

Presence of macular ectopia, retinal pathologies, and amblyopia were the most strongly correlated risk factors for strabismus development in ROP patients. DFD was not associated with severity of strabismus. Exotropia was mostly related to higher DFD and a possible relationship between esotropia and lower VA was encountered.

Introduction

Improved neonatal care has increased the survival rate of preterm infants, but this reduced mortality has resulted in an increase in the number of infants who may have long-term medical sequelae [1]. Visual impairments due to disruption in development of the ocular structures are common in the preterm population [2, 3]. Some of the most common ophthalmologic complications related to preterm birth are retinopathy of prematurity (ROP) [4–8], strabismus [9], refractive error [10], and visual acuity (VA) impairment [3].

ROP is a vasoproliferative disease of premature babies. Although in most cases it regresses spontaneously, ROP may result in serious sequelae when untreated and it stands as the main cause of blindness in childhood [11]. Long-term complications of ROP include visual impairment, myopia, anisometropia, strabismus, nystagmus, cataract, glaucoma, macular ectopia, and retinal detachment [11, 12].

The rate of strabismus is higher in preterm infants compared to full-term infants, particularly in those with more severe acute-phase ROP [13, 14]. Other risk factors reported in previous studies for strabismus in preterm infants are abnormal fixation behaviour, history of amblyopia, abnormal eye structure, neurodevelopmental anomalies, anisometropia, low gestational age (GA), and low birth weight (BW) [9, 13–15].

Macular ectopia may occur as a result of vitreoretinal fibrosis in preterm infants who have cicatricial retinopathy due to severe ROP. Although VA is widely variable in patients with macular ectopia, in general lower visual scores are expected in comparison to disease-free subjects [16]. There is a lack of data about the relationship between the extent of macular displacement and the degree of strabismus in the current literature.

The aim of this study is to examine the factors associated with strabismus in patients with ROP and to determine if there is a relationship between the severity of strabismus and macular ectopia.

Material And Methods

This study was carried out in an ROP referral centre and the medical records of patients followed for ROP between June 2002 and March 2018 were evaluated retrospectively. The research was approved by the local ethics committee.

Medical records of all ROP patients with either spontaneous regression or laser or vitreoretinal surgery for stage 4–5 ROP were reviewed for the inclusion criteria. Patients under the age of 18 with at least 1 year of follow-up were included in the study. Patients with neurological sequelae that may lead to visual impairment such as intraventricular haemorrhage, mental motor retardation, or cranial nerve palsy were excluded from the study. Patients were divided into three groups: Group 1, patients with spontaneous regression; Group 2, patients who had not undergone surgery and had received either unilateral or bilateral laser photocoagulation (LPC); and Group 3, patients who had undergone surgical treatment for ROP in one or both eyes. Group 3 was divided into two subgroups as Group 3a (patients with stage 4A ROP) and Group 3b (patients with stage 4B or stage 5 ROP). The treatment modalities and long-term complications were evaluated. Classification of ROP was done in accordance with the International Classification of Retinopathy of Prematurity (ICROP) revisited [8].

Evaluation of VA was performed with an E-chart, Lea figures, or Snellen chart if possible and converted to LogMAR. For patients who could not perform standard chart tests, fixation and following an object (FF) was assessed.

The presence, pattern, and amount of heterotropia were determined by the Hirschberg test, the Krimsky method, and the prism cover test (PCT). Cycloplegic refraction measurements were made with the use of a retinoscope (Heine Optotechnik GmbH & Co., Gilching, Germany) or handheld autorefractometer (Retinomax, Nikon Corp., Tokyo, Japan) following three consecutive applications of topical tropicamide (Tropamid 1%, Bilim İlaç, Istanbul, Turkey) or cyclopentolate (Sikloplejin, Abdi İbrahim, Istanbul, Turkey) after 60 min. A refractive error difference of > 2.00 D between eyes was accepted as anisometropia. Amblyopia was defined as objection to ocular occlusion or failure to initiate or maintain fixation with interocular difference of two or more lines in VA testing. Aphakic eyes were excluded in statistical analysis of the refractive errors in order to standardise the refraction measurements.

Macular ectopia and other retinal pathologies were determined by standard fundus examination with binocular indirect ophthalmoscopy using a 20 D lens. Imaging of the fundus was available only for those with clinically obvious macular ectopia by Zeiss Visucam 500 (Carl Zeiss Meditec Inc., Oberkochen, Germany), Nikon Optos (Nikon Corp., Tokyo, Japan), or Natus Retcam III (Natus Medical Inc., Pleasanton, CA, USA) devices. The disc-to-fovea distance (DFD), which is the distance between the centre of the fovea and the centre of the disc, was measured in millimetres using the manual calibre measurement software of the particular device. The relationship between and degree and type of strabismus and DFD were evaluated in patients who had macular ectopia and VA of at least counting fingers at 3 meters in both eyes.

The SPSS 21.0 software program (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The chi-square test was used to analyse the qualitative data. In the analysis of the factors affecting strabismus, binary logistic regression was performed and results were presented as odds ratios. The relationship status of the quantitative data was analysed by Pearson correlation. One-way ANOVA testing was used to compare DFD and VA between orthophoric and strabismic patients, and to compare VA and spherical equivalent states between treatment groups. Bonferroni correction was used for multiple post hoc comparisons. Values of $P < 0.05$ were considered statistically significant.

Table 1. Basic characteristics of the patients

Average ± standard deviation (minimum-maximum)

	GA at birth, weeks	BW, g	Age, years
Group 1 n=45	29.12±2.53 (24-34)	1.214±555.5 (660-2.500)	4.27±3.6 (1-13)
Group 2 n=70	27.88±2.39 (22-34)	1.161±405 (600-2250)	5.25±2.79 (1-12)
Group 3 n=91	28.35±2.87 (23-36)	1.223±422 (580-2.500)	4.30±2.89 (1-13)
	p=0.063*	p=0.698*	p=0.110*

*Chi-square test

Results

A total of 206 ROP patients were included in the study. Of these patients, 95 (46%) were female and 111 (53%) were male. There was no significant difference between the groups for GA, BW, or current age. Demographic characteristics of the patients in each group are presented in Table 1.

The stage of ROP differed between groups. Most of the patients in Group 1 had stage 1 ROP (75.5%), while patients in Group 2 had mainly stage 3 ROP (84.2%), and Group 3 consisted of the most severe ROP cases (stages 4A (39.5%), 4B (40.6%), and 5 (19.7%)).

The mean spherical equivalent of the patients was + 0.20 ± 2.90 D (-9.00 to + 8.00 D, median: 0.50 D) in Group 1, -1.71 ± 5.13 D (-2.00 to + 12.50 D, median: -5.00 D) in Group 2, -4.37 ± 4.06 (-11.00 to + 7.50 D, median: -0.75 D) in Group 3a, and − 3.62 ± 3.47 (-15.00 to + 0.50, median: -3.00 D) in Group 3b. Multiple post hoc comparisons with Bonferroni correction revealed that the mean spherical equivalent was lowest in Group 1 ($p < 0.001$) (Table 2).

Table 2
Comparison of the mean spherical equivalent and VA states between groups

	Spherical equivalent (D), mean ± SD (min-max)	**VA (LogMAR), mean ± SD**
Group 1	+ 0.20 ± 2.90 D (-9.00 to + 8.00 D)*	0.093 ± 0.254
	n = 41	n = 31
Group 2	-1.71 ± 5.13 D (-22.00 to + 12.50 D)	0.345 ± 0.497
	n = 58	n = 55
Group 3a	-4.37 ± 4.06 (-11.00 to + 7.50 D)	0.55 ± 0.37
	n = 27	n = 14
Group 3b	-3.62 ± 3.47 (-15.00 to + 0.50)	0.98 ± 0.39*
	n = 18	n = 18
	p < 0.001	p < 0.001
ANOVA		
Adjusted for multiple comparisons: Bonferroni		
*Statistically significant differences between marked group and other groups after post hoc multiple comparisons		

The mean VA among patients for whom the Snellen chart could be used was 0.093 ± 0.254 LogMAR (n = 31) in Group 1, 0.345 ± 0.497 LogMAR (n = 55) in Group 2, 0.55 ± 0.37 LogMAR (n = 14) in Group 3a, and 0.98 ± 0.39 LogMAR (n = 18) in Group 3b. The mean VA was found to be significantly lower in Group 3b compared to the other groups by multiple post hoc comparisons with Bonferroni correction ($p < 0.001$). Patients whose VA could not be measured with charts were evaluated for FF, which was positive in 27 of 28 eyes (96.42%) in Group 1, 28 of 30 eyes (93.33%) in Group 2, and 98 of 118 eyes (83.05%) in Group 3. Comparisons of spherical equivalent and VA states between groups are demonstrated in Table 2.

Rates of anisometropia, amblyopia, and nystagmus were significantly higher in Group 3 compared to the other groups ($p < 0.001$). Rates of retinal pathologies that cause visual impairment, such as total retinal detachment, diffuse scar at the posterior pole, and pale optic nerve, and presence of macular ectopia were also significantly higher in patients in Group 3 ($p < 0.001$). Comparisons of the incidence of the long-term sequelae of ROP among groups are summarised in Table 3.

Table 3
Distribution of the long-term sequelae of ROP among groups

Pathology	Group 1, n (%)	Group 2, n (%)	Group 3, n (%)	Total, n (%)	p* value
Anisometropia	12 (26.7%)	20 (28.6%)	68 (74.7%)	100 (48.5%)	< 0.001
Amblyopia	13 (28.9%)	26 (40.6%)	71 (85.5%)	110 (53.3%)	< 0.001
Nystagmus	2 (4.7%)	4 (5.7%)	30 (42.3%)	36 (17.4%)	< 0.001
Aphakia	0	0	31 (43.1%)	31 (15%)	-
Macular ectopia	5 (11.4%)	20 (28.6%)	64 (71.9%)	89 (43.2%)	< 0.001
Retinal pathologies	0	3 (4.3%)	49 (55.7%)	52 (25.2%)	< 0.001
*Chi-square test					

Strabismus was diagnosed in 94 of 206 (45.6%) patients overall. The incidences of strabismus in Group 1 and Group 2 were 28.9% and 31.4%, respectively. Strabismus was present in 69% of the patients in Group 3, and this rate was significantly higher compared to other groups ($p < 0.001$). Comparisons of the types of strabismus diagnosed in the groups are provided in Table 4.

Table 4
Comparison of the type of strabismus between groups

Type of strabismus	Group 1	Group 2	Group 3	Total	p* value
Esotropia	9 (20%)	15 (22.4%)	48 (55.2%)	72 (34.9%)	< 0.001
Exotropia	4 (8.9%)	6 (9%)	12 (13.8%)	22 (10.6%)	< 0.001
Total	13 (28.9%)	21 (31.4%)	60 (69%)	94 (45.6%)	< 0.001
*Chi-square test					

Anisometropia, amblyopia, aphakia, nystagmus, macular ectopia, and retinal pathologies were found to be more common in all patients with strabismus included in the study ($p < 0.05$) (Table 5). Among these pathologies, multivariate analysis determined amblyopia ($p = 0.012$), macular ectopia ($p = 0.005$), and retinal pathologies ($p = 0.005$) as the strongest risk factors for strabismus. In patients with amblyopia, strabismus was seen 2.9 times more (odds ratio: = 3.108; confidence interval: 1.4–6.1). In patients with macular ectopia, strabismus was seen 2.8 times more (odds ratio: 2.82; confidence interval: 1.4–5.8). In patients with retinal pathologies, strabismus was seen 2.7 times more (odds ratio: 2.71; confidence interval: 1.1–6.7).

Table 5
The relationship of strabismus with the long-term sequelae of ROP

Pathology	Strabismus, n (%)	Orthophoric, n (%)	p* value
Anisometropia	60 (61.8%)	37 (38.1%)	0.005
Amblyopia	67 (64.4%)	37 (35.5%)	< 0.001
Aphakia	25 (75.7%)	8 (24.2%)	< 0.001
Nystagmus	20 (66.6%)	10 (33.3%)	0.009
Macular ectopia	57 (66.2%)	29 (33.7%)	< 0.001
Retinal pathology	36 (73.4%)	13 (26.5%)	< 0.001
*Chi-square test			

Macular ectopia could be measured from coloured fundus pictures for 40 patients. Fifteen of the patients were orthophoric, and 20 and 5 patients had esotropia and exotropia, respectively. The mean DFD was 6.22 ± 1.67 (3–13) mm and the mean amount of strabismus was 18.90 ± 17.23 (0–50) PD in patients who had macular ectopia. There was no correlation between DFD and the amount of strabismus in this patient group (p = 0.364). The mean DFD in patients with esotropia was similar to that of orthophoric patients (5.77 mm and 5.92 mm, respectively). However, the mean DFD in patients with exotropia was significantly higher (7.69 mm) when compared to orthophoric and esotropic patients (p = 0.001).

The mean average VA of both eyes of those for whom a Snellen chart could be used among patients with macular ectopia was 0.169 ± 0.278 LogMAR (n = 6) in orthophoric patients, 0.61 ± 0.463 LogMAR (n = 12) in patients with esotropia, and 0.513 ± 0.325 LogMAR (n = 3) in patients with exotropia. The mean VA was significantly higher in orthophoric patients compared to those with esotropia and exotropia (p = 0.027). Comparison between the non-fixating eyes also revealed significantly higher VA in orthophoric patients compared to patients with esotropia and exotropia (p = 0.033). Patients with esotropia had lower VA compared to patients with exotropia, but the difference did not reach statistical significance (p = 0.729).

Discussion

Prematurity has a certain impact on the presence of refractive errors in children due to the disturbance in ocular growth [7]. Mild ROP does not contribute to refractive errors originating from prematurity, but children who are treated for severe ROP have the highest risk of developing refractive impairments, particularly myopia [17]. The prevalence of high myopia was shown to be positively correlated with increased severity of ROP and lower BW in the multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) [18]. In the Extremely Preterm Infants in Sweden Study (EXPRESS), Holmström et al. showed that patients with a GA of less than 27 weeks who had been treated for ROP had the

highest risk of developing eye and visual abnormalities [19]. Suggestions about the effects of the treatment on myopia have been controversial; the studies of Quinn et al. and Connoly et al. revealed that severe ROP itself is the main cause of myopia and the treatment does not make any additional contribution to the process [10, 20]. The results in the present study were compatible with the current literature. Myopia was significantly more common in patients with advanced ROP requiring surgery (Group 3) in our series ($p < 0.001$).

In their prospective study of 10-year-old prematurely born children, Larsson et al. found the rate of anisometropia of 1 to 2 D to be 3.8% and 0.9% for preterm and fullterm births, respectively [17]. In the same study ≥2 D anisometropia was present in 5.2% of the preterm births and the risk was maximum in cryotreated ROP patients (28%). Gursoy et al. reported the incidences of > 1.00 D anisometropia as 14% in stage 1 ROP, 18% in stage 2 or 3 ROP without indication for treatment, and 48% among patients who received treatment for ROP [21]. Ziylan et al. suggested significantly higher rates of anisometropia in patients with treshold ROP who recieved transpupillary diode LPC treatment (43.1%) compared to subjects with spontaneously regressed ROP (6.9%) [22]. In the present series, > 2.00 D refractive error difference was accepted as anisometropia with regard to ETROP outcome measures [13]. In our se[23]ries the rate of anisometropia was significantly higher in patients with severe ROP treated with vitreoretinal surgery (Group 3) compared to less severe ROP patients treated with LPC (Group 2) and to those with spontaneous regression (Group 1). The incidence of amblyopia was also higher in Group 3 compared to the other groups, which was thought to be related to the high rates of advanced-stage ROP, anisometropia, strabismus, and aphakia among patients in this group.

Risk factors for the development of strabismus are premature birth, severe ROP, low BW, and neurological abnormalities [14, 24–26]. VanderVeen et al. reported strabismus in the first year of life in 14.7% of preterm infants whose BW was < 1251 g [13]. A population-based study on the natural course of strabismus up to 10 years revealed that the onset of strabismus was after 3.5 years in one-third of the children [26]. In a follow-up study, the prevalence of strabismus at the age of 10 to 12 years was found to be about 3% in the normal population, while the rate was as high as 20% in prematurely born children [24]. There is a significant correlation between the presence of ROP and development of strabismus [13]. It has also been reported that the prevalence of strabismus increases with the increasing stages of ROP [24]. Sahni et al. reported that strabismus develops in 50% of children with stage 3 ROP [15]. Various studies revealed high rates of strabismus in patients who had previously received treatment due to severe ROP. Strabismus was present in 36% of patients who had received cryotherapy due to severe ROP in a population-based study [26]. The rate of strabismus was reported as 30% at the age of 9 months and increased to 42.2% through 6 years of age in the participants of the ETROP randomised trial. The cumulative prevalence has been reported as 59.4% [9, 13], while the overall rate of strabismus was 45.6% in our series. The incidence was 28.9% in the spontaneous regression group and 31.4% in the laser-treated group. The rate was significantly higher in the surgical treatment group (69%). Among 94 strabismic patients, 72 (76.5%) had esotropia and 22 (23.4%) had exotropia. This is compatible with the findings of Holmström et al., who reported esotropia in 77.4% and exotropia in 22.6% of preterm children [27]. Exotropia is even more infrequent in the normal population; the higher rate in prematurely born

children is attributed to the high prevalence of accompanying neurological disorders in these individuals [24, 26].

Abnormal fixation behaviour, amblyopia, and abnormal structure in one or both eyes were found to be positively associated with strabismus at both 1 year and 6 years of age. Furthermore, a history of anisometropia is also positively associated with strabismus [9, 13, 15, 23]. In the present study, anisometropia, amblyopia, aphakia, nystagmus, macular ectopia, and retinal pathologies were significantly more common in patients with strabismus. Among these pathologies, multivariate analysis revealed that amblyopia, macular ectopia, and retinal pathologies were the strongest risk factors for strabismus. The rate of strabismus was 2.9 times higher in patients with amblyopia, and strabismus was 2.8-fold and 2.7-fold more common in patients who had macular ectopia and retinal pathologies, respectively.

Various neurological abnormalities are associated with strabismus and visual loss in preterm births [14, 25, 28]. In extremely preterm children, visual impairment and blindness may be due to retinal or cerebral abnormalities or a combination of both. In order to compose homogeneous groups, patients with neurological disorders that may lead to a visual impairment such as intraventricular haemorrhage, mental motor retardation, or cranial nerve palsy were excluded from this study.

Macular ectopia may occur as a result of vitreoretinal fibrosis in preterm infants who have cicatricial retinopathy due to severe ROP. The present study shows the significant correlation between macular ectopia and strabismus. We further hypothesised that an abnormal DFD may be associated with the degree of strabismus. To the best of our knowledge, there are no data about this relationship in the current literature. A particular group of patients with macular ectopia and VA of at least counting fingers at a distance of 3 meters in both eyes were evaluated for correlation analysis. The mean DFD was 6.22 ± 1.67 (3–13) mm and the mean degree of strabismus was 18.90 ± 17.23 (0–50) PD in this group of patients. There was no statistically significant correlation between DFD and the severity of strabismus. In their study, Williams and Wilkinson reported the average DFD as 4.93 ± 0.33 mm and 4.88 ± 0.36 mm in the right and left eyes in 446 normal adults aged 20–30 years [29]. De Silva et al. examined DFD in the routine screening of 51 infants aged from 32 to 50 postmenstrual weeks. They reported the average DFD in these infants as 4.4 ± 0.4 mm [30]. In the present series, the mean DFD in patients who had macular ectopia was higher than the normal limits determined by the aforementioned studies. In patients with exotropia, DFD was significantly higher (7.69 mm) when compared to that of esotropic and orthophoric patients ($p = 0.001$), which may support the idea that exotropia may be secondary to the slippage of the visual axis towards the temporal retina. However, DFD did not have an impact on the severity of strabismus.

In patients with esotropia, DFD was similar to that of the orthophoric patients (5.77 mm and 5.92 mm, respectively). VA scores were significantly worse in patients with esotropia and exotropia compared to the orthophoric patients ($p = 0.027$). The fact that many patients with macular ectopia were orthophoric suggests that macular ectopia can be tolerated to a certain extent if the VA is good enough. Although the

mean DFD of the patients with esotropia was similar to that of the orthophoric patients, macular ectopia was not as well tolerated as in orthophoric patients, presumably due to the significantly low VA in patients with esotropia compared to the orthophoric patients. Although the difference was not statistically significant, VA in patients with esotropia was even lower than that of the patients with exotropia; thus, it can be speculated that esotropia may be related to low VA.

This is the first study showing a relationship between strabismus and macular ectopia in children with ROP sequelae. However, there are some limitations, including the retrospective nature of the study and the limited number of patients in the subgroups. Further prospective studies with larger series are required to make more precise determinations about the relationship between strabismus and macular ectopia in children with ROP sequelae.

In conclusion, functional outcomes were the best in patients with spontaneous regression, and satisfying results were also obtained in patients who were treated with LPC for moderate stages of ROP. Worst outcomes and the highest rates of long-term complications like nystagmus, strabismus, amblyopia, anisometropia, and macular ectopia were recorded in patients who had advanced ROP and required surgical treatment. The prevalence of strabismus was correlated with the severity of ROP. Presence of macular ectopia, retinal pathologies, and amblyopia were the most strongly correlated risk factors for strabismus development in ROP patients. Exotropia was mostly related to higher DFD and a possible relationship between esotropia and lower VA was encountered.

Declarations

Disclosure Statement

The authors have no conflicts of interest to declare.

Ethical Approval

All procedures performed in this study were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethics committee approval was obtained from Gazi University (Research code: 2017/469. Date:19.12.2017/10). Informed consent was not obtained because of the retrospective nature of the study.

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Author Contributions

SŞK: Conception and design, data analysis; manuscript draft and revision of the manuscript.

HTA: Conception and design, data analysis supervision; revision of the manuscript.

ŞÖ: Conception and design, critical senior supervision of the study; revision of the manuscript.

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