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Astigmatism Progression in the Early Treatment for Retinopathy of Prematurity Study to 6 years of age

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Abstract

Purpose—To examine the prevalence of astigmatism (≥1.00 diopter (D)) and high astigmatism (≥2.00 D) from 6 months post term due date to 6 years postnatal, in preterm children with birth weight ≤ 1251g who developed high-risk prethreshold retinopathy of prematurity (ROP) and participated in the Early Treatment for ROP (ETROP) Study.

Design—Observational Cohort Study

Participants—401 infants who developed high-risk prethreshold ROP in one or both eyes and were randomized to early treatment (ET) versus conventional management (CM). Refractive error was measured by cycloplegic retinoscopy. Eyes were excluded if they received additional retinal, glaucoma, or cataract surgery.

Intervention—Eyes were randomized to receive laser photocoagulation at high-risk prethreshold ROP or to receive treatment only if threshold ROP developed.

Main Outcome Measures—Astigmatism and high astigmatism at each study visit.

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[7]A list of the members of the Early Treatment for Retinopathy of Prematurity Cooperative Group can be found in Archives of Ophthalmology 2003;121:1684-96.

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This article contains online-only material. The following should appear online-only: Figures 1-5

Results—For both ET and CM eyes, there was a consistent increase in prevalence of astigmatism over time, increasing from 42% at 4 years to 52% by 6 years for the group of ET eyes and from 47% to 54% in the CM eyes. There was no statistically significant difference between the slopes (rate of change per month) of the ET and CM eyes for both astigmatism and high astigmatism. (P=0.75)

Conclusions—By 6 years of age, over 50% of eyes with high-risk prethreshold ROP developed astigmatism ≥ 1.00 D, and nearly 25% of such eyes had high astigmatism (≥ 2.00 D). Presence of astigmatism was not influenced by timing of treatment, zone of acute-phase ROP, or presence of plus disease. However, there was a trend toward higher prevalence of astigmatism and high astigmatism in eyes with ROP residua. Most astigmatism was with-the-rule (75º –105º). More eyes with Type 2 than Type 1 had astigmatism by 6 years. These findings reinforce the need for follow-up eye examinations through early grade school years in infants with high risk prethreshold ROP.

Keywords

astigmatism; refractive error; prematurity

Introduction

Initial results from the Early Treatment of ROP (ETROP) study indicated that the structural and functional outcome of eyes with ROP up to three years of age could be improved if peripheral retinal ablation is performed at a severity of retinopathy less than classic “threshold,” i.e., at prethreshold severity that had been determined to be high risk for progressing to poor structural outcome.[1,2] The revised indications for the treatment of retinopathy of prematurity (ROP) resulting from Phase I of the ETROP randomized trial resulted in a significant change in clinical practice. The new clinical algorithm called for treatment of Type 1 ROP; i.e., eyes with Zone I, stage 3, or Zone I any stage and plus disease; and eyes with Zone II stage 2 or 3 and plus disease. Continued observation was recommended for the remaining prethreshold eyes, designated as Type 2 ROP. Results of Phase II of the ETROP trial showed that early treatment for Type 1 high-risk prethreshold eyes improved visual acuity outcomes at 6 years of age, and that early treatment for Type 2 high-risk prethreshold eyes did not.[3] This reinforced the clinical practice of treating eyes with Type 1 ROP at diagnosis, but not eyes with Type 2 ROP unless the ROP progressed to Type 1 severity.

Refractive error data up to 3 years of age of the ETROP trial has been reported, documenting both the prevalence of myopia and astigmatism up to three years of age.[4,5,6] Examination of astigmatism at 6 and 9 months corrected age and at 2 and 3 years postnatal age showed no difference in the prevalence of astigmatism (≥ +1.00 diopter (D)) or high astigmatism (≥ +2.00 D) in eyes treated at high-risk prethreshold ROP (early treated, ET) compared to eyes that were managed conventionally with treatment at threshold if ROP progressed (conventionally managed, CM).[6] However, prevalence of astigmatism in both the ET and CM groups increased from 32% at 6 months to 42% by 3 years, mostly occurring between 6 and 9 months. By 3 years, nearly 20% of ET eyes had high astigmatism. At least until age 3 years, zone of acute-phase ROP, presence or absence of plus disease, and retinal residua of ROP (straightened temporal vessels or macular heterotopia) had little effect on prevalence of astigmatism or high astigmatism, and axis of astigmatism and high astigmatism was most often "with-the-rule."

The purpose of the present paper is to extend this analysis of astigmatism and high astigmatism in this group of preterm infants who continued participation in the Early

Treatment for ROP (ETROP) Study. We report the prevalence and associations with astigmatism up to 6 years of age in this cohort.

Participants and Methods

401 infants with birth weight ≤ 1251g were enrolled in the ETROP Study at one of 26 participating centers in the U.S. between October 1, 2000 and September 30, 2002.[2] Randomized infants had developed high-risk prethreshold ROP in one or both eyes with a risk ≥ 0.15 of a poor structural outcome at three months post term.[1] In the 317 infants who developed high-risk prethreshold ROP in both eyes, one eye was randomly assigned to treatment within 48 hours (ET) and the fellow eye was observed until regression occurred or until threshold ROP developed and was treated (CM). Of the 84 infants who developed high-risk prethreshold ROP in only one eye, 44 eyes were randomized to ET while 40 eyes were randomized to CM. The study protocol was approved by the Review Boards of all participating institutions. Parents or guardians of all participants gave informed consent prior to enrollment and upon entry into the follow-up phase (Phase II) of the Study. Study design details have been published previously.[1,2,7] At all study ages, cycloplegic retinoscopy was performed by study-certified examiners. 1% cyclopentolate hydrochloride was used as the cycloplegic agent unless there was a medical contraindication, in which case either 0.5% cyclopentolate or 1% tropicamide was used.

Astigmatism and high astigmatism were defined as plus cylinder of ≥ 1.00 diopter (D) and ≥ 2.00 D, respectively. Astigmatism was further classified as with the rule (WTR) (75º – 105º), against the rule (ATR) (0º – 15º and 165º – 180º), and oblique (OBL) (16º – 74º and 106º – 164º). Prevalence rates were computed by eyes with ≥ 1.00 D and ≥ 2.00 D cylinder divided by eyes with valid refraction.

The percentage of participants with astigmatism was categorized in two ways: eyes with greater than or equal to 1.00D (Figure 1A, available at http://aaojournal.org) and eyes with greater than or equal to 2.00D (Figure 1B, available at http://aaojournal.org). To further examine the trend over time and slope of astigmatism, we used the Theil regression technique that does not require the assumption that percentages follow normal probability distributions.[15] The slope was estimated by the median of the pairwise slopes. The technique calculates the slope per month for all possibilities between data points over time and assesses the median of the slopes of each treatment group. To test formally the equality of the slopes between the treatment and the conventional management group, we used the Sen-Adichie test.[15]

Results

This report includes data from refractive assessment of 262 ET and 239 CM eyes at 4 years, 255 ET treated and 233 CM eyes at 5 years, and 279 ET and 257 CM eyes at 6 years. Data excluded from this analysis are data from participants who died prior to the prior to the study examination (29 at 4 years, 30 at 5 years, and 31 at 6 years), participants who did not attend the yearly study examination (53 at 4 years, 58 at 5 years, and 28 at 6 years), eyes that were unable to be refracted due to retinal detachment, media opacity, pupillary miosis, or other difficulty in refracting (14 ET and 25 CM eyes at 4 years, 14 ET and 23 CM eyes at 5 years, and 15 ET and 26 CM eyes at 6 years), or eyes that had undergone vitrectomy, scleral buckling procedures, iridectomy, glaucoma procedures, or cataract surgery (13 ET and 18 CM eyes at 4 years, 16 ET and 20 CM eyes at 5 years, and 16 ET and 20 CM eyes at 6 years).

Prevalence of Astigmatism and High Astigmatism (Table 1)

The prevalence of astigmatism at each test age was similar in ET and CM groups. The differences between the ET and CM eyes were not statistically significant for any of the three time points (for Astigmatism: 4 years P=0.12, 5 years P=0.98 and 6 years P=0.57; for High Astigmatism: 4 years P=0.53, 5 years P=0.71 and 6 years P=0.42). For both ET and CM eyes, there was a small increase in prevalence of astigmatism over time, increasing from 42% at 4 years to 52% by 6 years for the group of ET eyes and from 47 to 54% in the CM eyes. For the group of ET eyes, prevalence of high astigmatism showed an increase at each successive examination age between 4 and 6 years, increasing from 18% to 23%. The CM group of eyes showed an increase in prevalence of high astigmatism from 18 % to 25% over the same time frame.

Within the group of CM eyes (rightmost two columns of Table 1), the prevalence of astigmatism and high astigmatism was higher in eyes that progressed to threshold severity and underwent peripheral retinal ablation, compared to eyes in which the ROP regressed without reaching threshold.

Using the Theil regression technique for eyes with greater than or equal to 1.00 D of astigmatism (Figure 1A), the median slopes for ET eyes was 0.28 per month (95% CI 0.17, 0.40) and 0.32 per month (95% CI 0.18, 0.37) for CM eyes. The Sen-Adichie test for the equality in the two median slopes showed no difference between the two groups (0.68, 0.41). Similarly, for the group of eyes with greater than or equal to 2.00 D of astigmatism (Figure 1B), the median slopes for the 2 groups were 0.17 and 0.22 for the ET and CM groups, respectively. The 95% percent confidence intervals were (0.08, 0.32) and (0.06, 0.35), respectively. The observed value of the Sen-Adichie test was 0.10 (P = 0.75). Therefore, there was no statistically significant difference between the slopes of the ET and CM eyes for both Diopter greater than or equal to 1.00 or greater than or equal to 2.00.

Astigmatism, High Astigmatism, and Location of Acute-Phase ROP

Figure 2 (available at http://aaojournal.org) presents the prevalence of astigmatism (Figures 2A and 2B) and high astigmatism (Figures 2C and 2D) at 4, 5 and 6 years of age, stratified by location (zone I vs. zone II) of the acute-phase retinopathy. As shown in Figure 1, among the eyes that could be refracted, prevalence of astigmatism was similar in eyes with zone I ROP and eyes with zone II ROP, as was prevalence of high astigmatism. Furthermore, eyes in the ET group and eyes in the CM group showed a similar prevalence of astigmatism and high astigmatism within zone I and zone II.

Astigmatism, High Astigmatism, and Presence of Plus Disease

Figure 3 (available at http://aaojournal.org) presents the prevalence of astigmatism (Figures 3A and 3B) and high astigmatism (Figures 3C and 3D) at 4, 5 and 6 years of age, stratified by the presence or absence of plus disease. For the eyes that could be refracted, prevalence of astigmatism and prevalence of high astigmatism were similar in ET and CM eyes with and without plus disease.

Astigmatism, High Astigmatism, and Retinal Residua of ROP

Figure 4 (available at http://aaojournal.org) presents the prevalence of astigmatism (4A, 4B, and 4C) and high astigmatism (4D, 4E, and 4F) at 4, 5 and 6 years of age, stratified by severity of ROP residua. Prevalence of astigmatism is higher for both ET and CM eyes with macular heterotopia. The prevalence of high astigmatism in eyes with straightened vessels and macular heterotopia was greater in CM eyes than ET eyes at each age.

Astigmatism, High Astigmatism, and Axis of Astigmatism

At each of the yearly examinations, eyes with astigmatism ≥ 1.00 D were much more likely to have WTR astigmatism than ATR or OBL astigmatism (Figure 5, available at http://aaojournal.org), and there was little difference in the type of axis of astigmatism seen between ET and CM eyes. The same was found with eyes having high astigmatism, although the proportion of eyes with ATR astigmatism was less in CM than ET eyes.

Astigmatism, High Astigmatism, and Type 1 vs Type 2 ROP

The prevalence of astigmatism at 6 years in ET and CM eyes with Type 1 ROP was 49.7% and 52.2% respectively. For eyes with Type 2 ROP, the prevalence of astigmatism was 57.5% regardless of the timing of treatment. High astigmatism was found in 22.1% of ET eyes and 23.9% of CM eyes with Type 1 ROP and 23.8% of ET eyes and 28.8% of CM eyes with Type 2 ROP.

Discussion

The results of the ETROP Study indicated that early treatment of eyes with high-risk prethreshold ROP provided better visual function and retinal structural outcomes, compared to conventional management, in which eyes were treated if they reached threshold severity.[2,3] In a previous paper that reported data from the ETROP Study up to 3 years of age, the prevalence of astigmatism was similar between ET and CM eyes, and for both groups, the prevalence of astigmatism increased from 32% at 6 months to 42% by 3 years. Most of this change occurred between the 6 and 9 month study examinations.[6] By 3 years, nearly 20% of ET eyes had high astigmatism. Astigmatism was not influenced by zone of ROP, plus disease, or ROP residua and was most often characterized as "with-the-rule."

The results of the present study extend our finding that, by 6 years of age, over 50% of eyes with high-risk prethreshold ROP were likely to develop astigmatism ≥ 1.00 D, and nearly 25% of eyes had high astigmatism (≥ 2.00 D). For comparison, the prevalence rates of eyes with threshold ROP from the CRYO-ROP study was approximately 60% of all treated and control eyes with astigmatism ≥1.00 D and approximately 30% of such eyes with high astigmatism (≥ 2.00 D) by 5.5 years of age.[8] To put these findings into context, a survey of reported prevalence rates of astigmatism of ≥ 1.00 D found 44% in 3- to 5-year-old Native American children,[9] 28.4% in American children,[10] nearly 22 % in Canadian children (mean age 51.1 months),[11] 21.1% in preschool children from Hong Kong,[12] 4.8% in 6-year old Australian children,[13] and 11.4% in Taiwanese children > 6 years old.[14] The prevalence of astigmatism in our cohort of high-risk prethreshold eyes was significantly higher than the prevalence of astigmatism in any of these “normal” populations.

Earlier treatment of eyes with high-risk prethreshold ROP did not influence the development of astigmatism, nor did ROP in Zone I or the presence of plus disease. Eyes with residua of ROP, either straightened vessels or macular heterotopia, appeared to have a higher prevalence of astigmatism or high astigmatism compared with eyes with normal appearing posterior poles, although this was not statistically significant. The majority of astigmatic eyes had WTR astigmatic axis, and the axis of astigmatism was oblique in approximately 20% of eyes, with little change over time. The same was found with eyes having high astigmatism, although the proportion of eyes with ATR astigmatism was less in CM than ET eyes.

It is important to remember that eyes randomized into the ETROP Study were a select subset of eyes at-risk for ROP and were included only if prethreshold ROP was present and were determined to be at high risk for an unfavorable outcome based on the RM-ROP2 risk management program.[1] This RM-ROP2 algorithm takes into account race, birth weight,

gestational age, location and timing of onset of ROP, speed of progression and severity of acute-phase ROP.[2] Therefore, the results of our analysis of astigmatism in eyes with acute-phase ROP may have limited generalizability.

At the present time, the decision to treat ROP is determined by the presence of Type 1 ROP, with Type 2 ROP requiring close evaluation. Acknowledging the clinical importance of this new algorithm, we compared the prevalence of astigmatism and high astigmatism in these two groups. Interestingly, there was a higher prevalence of astigmatism in eyes with Type 2 ROP compared to eyes with Type 1 ROP, regardless of the timing of treatment. The explanation for this remains unclear.

In summary, these findings regarding astigmatism in infants who have been diagnosed with high risk prethreshold ROP reinforce the importance of follow-up eye exams through at least 6 years of age, as nearly half of these children are likely to have astigmatism ≥ 1.00D and a quarter are at risk of having high astigmatism ≥ 2.00D. Recognition of high astigmatism and/or astigmatism at oblique axis in these patients is important, as treatment of refractive amblyopia may be more successful with early intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Percentage of eyes with astigmatism and high astigmatism at 4, 5, and 6 years postnatal age.

Refractive status		Treatment at high-risk prethreshold n/N* (%)	Conventionally-managed high-risk eyes		
			Total conventionall y-managed high-risk eyes n/N* (%)	Treatment at threshold n/N (%)	Regressed, no treatment n/N (%)
Astigmatism greater than or equal to 1.00 Diopters	4 years	111/262 (42.4%)	112/239 (46.9%)	77/145 (53.1%)	35/94 (37.2%)
	5 years	124/255 (48.6%)	115/233 (49.4%)	79/141 (56.0%)	36/92 (39.1%)
	6 years	145/279 (52.0%)	138/257 (53.7%)	94/157 (59.9%)	44/100 (44.0%)
Astigmatism greater than or equal to 2.00 Diopters	4 years	47/262 (17.9%)	44/239 (18.4%)	30/145 (20.7%)	14/94 (14.9%)
	5 years	53/255 (20.8%)	52/233 (22.3%)	37/141 (26.2%)	15/92 (16.3%)
	6 years	63/279 (22.6%)	65/257 (25.3%)	47/157 (29.9%)	18/100 (18.0%)

*See Results Section for early treatment (ET) and conventional management (CM) eyes with unavailable refractive error data.