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Prevalence and Course of Strabismus in the First Year of Life for Infants With Prethreshold Retinopathy of Prematurity

Findings From the Early Treatment for Retinopathy of Prematurity Study

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Objective: To present strabismus data for premature infants with prethreshold retinopathy of prematurity (ROP) enrolled in the Early Treatment for Retinopathy of Prematurity study.

Design: The prevalence of strabismus was tabulated for all of the infants with high-risk prethreshold disease who participated in the randomized trial of the Early Treatment for Retinopathy of Prematurity study and were examined at 6 and/or 9 months' corrected age as well as for all of the infants with low-risk prethreshold disease who were examined at 6 months' corrected age.

Main Outcome Measures: Presence or absence of strabismus at 6 and 9 months' corrected age.

Results: The prevalence of strabismus at 6 months was higher for infants with high-risk prethreshold ROP than for those with low-risk prethreshold ROP (20.3% vs 9.6%, respectively; $P<.001$). Risk factors associated with the development of strabismus at 9 months include abnormal fixation behavior, presence of amblyopia, and outborn birth status (ie, born outside of a study-affiliated hospital). At 9 months, 30% of infants with high-risk prethreshold ROP had strabismus, although only 42% showed strabismus at 6 months. Thirty percent of infants with strabismus at 6 months showed normal alignment at 9 months.

Conclusions: Infants with high-risk prethreshold ROP show significant variability in the presence vs absence of strabismus in the first year of life; thus, conservative management is recommended.

Application to Clinical Practice: Ophthalmologists managing strabismus in infants who have high-risk prethreshold ROP should be aware of the significant variability in ocular alignment during the first year of life.

Arch Ophthalmol. 2006;124:766-773

STRABISMUS HAS BEEN REported to develop in the first year of life in 14.7% of preterm infants with birth weights less than 1251 g.[1] The rate of strabismus is higher for preterm infants who had more severe acute-phase retinopathy of prematurity (ROP) and also for infants with neurodevelopmental abnormalities.[1-5] Strabismus can cause abnormal binocularity and amblyopia, necessitating amblyopia therapy, spectacle wear, and/or surgical procedures.[6] Additionally, there may be psychosocial consequences from the cosmetic effect of misaligned eyes.[7,8]

This article reports strabismus data that were collected prospectively from 730 premature infants with birth weights less than 1251 g who were enrolled in the Early Treatment for Retinopathy of Prematurity study. All of the 730 infants developed prethreshold ROP during the neonatal period; 401 of them developed high-risk prethreshold ROP[9] and were enrolled in the randomized trial of early treatment for ROP.[10,11] Data were examined to compare the prevalence and type of strabismus at 6 and 9 months' corrected age for infants who developed high-risk prethreshold ROP and were enrolled in the randomized trial of early treatment for ROP as well the prevalence and characteristics of strabismus at 6 months' corrected age in infants with low- vs high-risk prethreshold ROP. Analyses were conducted to determine whether presence of strabismus

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was correlated with demographic variables, visual acuity measures, ocular structural outcomes, and anisometropic refractive status.

METHODS

Infants with birth weights less than 1251 g and birth dates between October 1, 2000, and September 30, 2002, were screened at 26 participating centers. All of the centers had the Early Treatment for Retinopathy of Prematurity study protocol reviewed and approved by their human ethics committees. Infants who developed prethreshold ROP and whose parents had consented to enrollment in the natural history portion of the Early Treatment for Retinopathy of Prematurity study were followed up to at least 6 months' corrected age (age from estimated due date). High-risk prethreshold ROP was determined by the RM-ROP2 model[9] based on results of examinations by 2 independent study-certified ophthalmologists. Infants who developed high-risk prethreshold ROP were eligible for the randomized trial of early treatment vs conventional management with treatment at threshold if threshold ROP was reached. All of the randomized infants were also examined at 9 months' corrected age to evaluate structural and visual outcomes. All of the examinations were performed by study-certified ophthalmologists. The details of these examinations and determination of eligibility for randomization have been published previously.[10,11]

At the 6- and 9-month examinations, visual acuity indicators (including fixation behavior and presence or absence of nystagmus), ocular alignment and motility status, cycloplegic refraction, and structural outcomes were recorded. Standard clinical methods to assess visual acuity as well as ocular motility and alignment were used, and observations were made while the patient was fully awake. Normal fixation was defined as central, steady, and maintained (CSM). Ocular alignment was classified as normal, abnormal, or unable to assess. If strabismus was present, it was classified as intermittent or constant and by the direction of the deviation (esotropia, exotropia, hypertropia, or any combination thereof). Some infants showed more than 1 direction of strabismus during a given examination. The magnitude of the deviation was not recorded. Children were deemed unable to assess if they were somnolent or in instances where findings were suspicious but inconclusive.

If significant refractive error or amblyopia was found at the 6-month examination, spectacle correction and/or amblyopia therapy was instituted. Amblyopia was defined as abnormal, unmaintainable fixation behavior in 1 eye in the absence of an unfavorable structural outcome (ie, retinal fold or detachment involving the macula, or retrolental mass) to satisfactorily explain poor fixation in 1 or both eyes. Amblyopia treatment was also instituted despite the presence of an unfavorable structural outcome at the discretion of the examining ophthalmologist.

At the 9-month examination, grating visual acuity was measured with Teller visual acuity cards, and results were designated as favorable or unfavorable.[12] The favorable group included eyes with visual acuity scores in the normal ($\geq$3.70 cycles per degree) and below normal (1.85 to $<$3.70 cycles per degree) categories, and the unfavorable group included eyes with lower visual acuity scores. All of the infants were tested with spectacle correction for significant refractive errors and, if amblyopia was suspected, after at least 4 weeks of amblyopia therapy.

Statistical tests were first performed using univariate analyses for each variable, and *P* values are given in the text. Then, multiple logistic regression analysis including all of the variables was performed to examine the association of factors with strabismus. The *P* values for the final model are included in this article.

RESULTS

Data for 96.8% of the 316 surviving infants with low-risk prethreshold ROP and for 94.8% of the 386 surviving randomized infants with high-risk prethreshold ROP were available for comparison at the 6-month examination. Data for 98.2% of the 379 surviving infants with high-risk prethreshold ROP were available at the 9-month examination.

Table 1 indicates the prevalence of strabismus at the 6-month examination for infants with low-risk prethreshold ROP and at 6 and 9 months for infants with high-risk prethreshold ROP. Strabismus was more likely to be present at 6 months in the high-risk prethreshold group compared with the low-risk prethreshold group (20.3% vs 9.6%, respectively; $P<.001$). Within each risk group, there were no statistically significant differences at 6 months in the prevalence of strabismus based on birth weight, gestational age at birth, race, sex, inborn (ie, born in a study-affiliated hospital) or outborn birth status, or single vs multiple birth status.

For infants with high-risk prethreshold ROP, strabismus was more common at the 9-month examination than at the 6-month examination (30.0% vs 20.3%, respectively; $P=.002$). At 9 months, the prevalence of strabismus was again not related to gestational age at birth, race, sex, or single vs multiple birth status. Although the prevalence of strabismus appears to be less for infants with a birth weight greater than 1000 g (6.3%) than for infants with a birth weight less than 750 g (30.4%) and between 750 and 1000 g (32.4%), this was not statistically significant after adjusting for other risk factors. Strabismus was more common in outborn infants than in those who were inborn (44.4% vs 26.4%, respectively; $P=.003$), even after adjusting for other baseline variables.

Strabismus was compared in the randomized infants who were seen at both the 6- and 9-month examinations to evaluate the short-term evolution of strabismus in infants with high-risk prethreshold ROP. A total of 357 infants with high-risk prethreshold ROP were seen at both the 6- and 9-month examinations, representing 94.2% of the cohort expected for this comparison. Strabismus was present in 107 (30.3%) of the 354 infants who could be assessed at 9 months compared with 66 (20.1%) of the 329 infants who could be assessed at 6 months. Of the 263 infants with normal alignment at 6 months, 45 (17.1%) had strabismus at the 9-month examination. Of the 66 infants with strabismus at 6 months, 20 (30.3%) showed normal alignment at the 9-month examination. The majority (68.2%) of the 66 infants with strabismus at 6 months continued to have strabismus at 9 months, and only 1 of these infants, an infant with intermittent strabismus, showed a change in the direction of the deviation. Seventeen (60.7%) of 28 infants who were classified as unable to assess at 6 months had strabismus during the 9-month examination. Inability to assess alignment at 6 months was associated with the inability to determine or the presence of abnormal fixation in 1 or both eyes, as only 1 infant among the 28 was CSM in both eyes. Of the 107 infants

Table 1. Prevalence of Strabismus at 6 and 9 Months

Baseline Characteristic	Infants in Low-Risk Prethreshold ROP Group			Infants in High-Risk Prethreshold ROP Group					
	6 mo			6 mo			9 mo		
	Total, No.	Strabismus, No. (%)	UA, No.*	Total, No.	Strabismus, No. (%)	UA, No.*	Total, No.	Strabismus, No. (%)	UA, No.*
Total	306	29 (9.6)	4	366	68 (20.3)	31	372	110 (30.0)	5
Birth weight, g									
<750	149	17 (11.5)	1	240	46 (20.6)	17	243	73 (30.4)	3
750-999	123	9 (7.5)	3	109	19 (19.8)	13	113	36 (32.4)	2
≥1000	34	3 (8.8)	0	17	3 (18.8)	1	16	1 (6.3)	0
Gestational age, wk									
≤27	244	24 (10.0)	4	323	58 (19.7)	28	329	97 (29.9)	5
>27	62	5 (8.1)	0	43	10 (25.0)	3	43	13 (30.2)	0
Race									
White	153	13 (8.6)	1	233	41 (19.2)	20	236	75 (32.1)	2
Black	91	9 (10.1)	2	69	17 (27.4)	7	67	19 (29.2)	2
Hispanic	39	4 (10.5)	1	50	9 (19.1)	3	55	15 (27.8)	1
Other	23	3 (13.0)	0	14	1 (7.7)	1	14	1 (7.1)	0
Sex									
Male	174	16 (9.3)	2	198	41 (23.2)	21	199	61 (31.3)	4
Female	132	13 (10.0)	2	168	27 (17.1)	10	173	49 (28.5)	1
Inborn†									
Yes	270	26 (9.8)	4	291	54 (20.1)	22	299	78 (26.4)	4
No	36	3 (8.3)	0	75	14 (21.2)	9	73	32 (44.4)	1
Single vs multiple birth									
Single	201	21 (10.6)	3	258	44 (18.9)	25	265	77 (29.5)	4
Multiple	105	8 (7.7)	1	108	24 (23.5)	6	107	33 (31.1)	1

Abbreviations: ROP, retinopathy of prematurity; UA, unable to assess.
*Those infants who were deemed unable to assess were not included in the percentage calculations.
†Born in study-affiliated hospital.

with strabismus at 9 months, only 42.1% had strabismus at the 6-month examination. Three infants underwent surgical intervention for strabismus between the 6- and 9-month examinations, but each of these infants continued to have strabismus at 9 months.

Esotropia was the most common form of strabismus at both the 6- and 9-month examinations. At the 6-month examination, 51 (75.0%) of the 68 infants with strabismus were esotropic, and at the 9-month examination, 79 (71.8%) of the 110 infants with strabismus were esotropic. Some infants (2 infants at 6 months and 2 infants at 9 months) showed more than 1 type of strabismus. One of these infants had Duane syndrome. More infants showed constant strabismus at the 9-month examination (62.7%) compared with the 6-month examination (44.1%).

Abnormal fixation behavior in 1 or both eyes was highly predictive of strabismus. In the 237 infants in whom fixation was CSM in both eyes, only 21 infants (8.9%) had strabismus, but in the 105 infants in whom fixation was not CSM in 1 or both eyes, 77 (73.3%) had strabismus ($P<.001$). There was little difference in the prevalence of strabismus between those infants with poor fixation in 1 eye only compared with poor fixation in both eyes (72.6% vs 80.0%, respectively). In the 291 infants with grating visual acuity that was classified as favorable in both eyes, 59 (20.3%) had strabismus whereas in the 75 infants with grating visual acuity that was classified as unfavorable in 1 or both eyes, 50 (66.7%) had strabismus ($P<.001$). Additionally, more infants who were diagnosed with amblyopia by the examining ophthalmologist at the 9-month examination (80.8%) had strabismus than those who were not diagnosed with amblyopia at either the 6- or 9-month examination (26.1%) ($P<.001$).

The prevalence of strabismus at 9 months was higher for randomized infants with an unfavorable structural outcome in 1 or both eyes compared with infants with a favorable structural outcome in both eyes (67.9% vs 22.8%, respectively; $P<.001$).

To compare the presence of anisometropic refractive status and strabismus, we calculated spherical equivalents for each eye, and we chose 2.00 diopters (D) of difference between eyes as significant anisometropia. There was a higher rate of strabismus for infants with anisometropia greater than 2.00 D than for those with less than 2.00 D of anisometropia (38.5% vs 21.0%, respectively; $P<.001$).

In the final regression analysis of data (**Table 2**), the 3 significant factors were fixation behavior ($P<.001$), amblyopia ($P=.02$), and inborn or outborn birth status ($P=.007$). Abnormal fixation behavior (not CSM) in 1 or both eyes was associated with a 15.3-time greater risk of strabismus, and the presence of amblyopia was associated with a 4.2-time greater risk of strabismus. Being inborn was protective, and it was associated with a 65% reduction in the odds of having strabismus.

COMMENT

Premature infants have a higher rate of strabismus than full-term infants.[1,13-21] Previous investigators have noted that as the severity of acute-phase ROP increases, the incidence of strabismus increases.[1,3,18,22-24] All of the infants in this study had prethreshold ROP, and there was a significantly higher prevalence of strabismus in infants randomized for high-risk prethreshold ROP than in infants who had low-risk prethreshold ROP when examined at 6 months' corrected age (20.3% vs 9.6%, respectively; $P<.001$). At 9 months' corrected age, 30.0% of the infants who had high-risk prethreshold ROP and were participants in the randomized trial had strabismus. Even among the subgroup of infants who had a favorable ocular structural outcome in both eyes at 9 months, 22.8% had strabismus.

Even though low birth weight and gestational age are correlated with a higher rate of more severe ROP and/or neurologic insult,[3,4,9] among this sample of infants with a birth weight less than 1251 g, there was no difference between prevalence of strabismus and gestational age or weight at birth. Outborn birth status was associated with a higher prevalence of strabismus at 9 months, although outborn birth status did not appear to be a significant factor at 6 months. Infants who were outborn and transferred to a referral center may represent infants who were the sickest and thus were at higher risk of developing more morbidity associated with their prematurity, but we could not explain why there was a difference at the 6- vs 9-month examinations regarding presence of strabismus.

Not surprisingly, infants with an abnormal visual acuity measure in 1 or both eyes were more likely to have strabismus than infants with normal visual acuity measures in both eyes. In the final analysis, there was a stronger association for abnormal fixation behavior in 1 or both eyes and presence of strabismus ($P<.001$) than for an unfavorable grating visual acuity result in 1 or both eyes and presence of strabismus ($P=.46$). Grating visual acuity tests may underestimate the presence of low vision, especially in patients with macular or cerebral visual impairment, and the range of normal grating visual acuity results in infancy includes values that correspond to low vision if measured in older children or adults.[25-28] The diagnosis of amblyopia was found to be highly correlated with the presence of strabismus, although no correlation with the cause of amblyopia was made. We could not evaluate whether amblyopia contributed to the development of strabismus or the strabismus contributed to the development of amblyopia for this group of infants. Anisometropia appeared to be predictive of strabismus, as did an unfavorable structural outcome in 1 or both eyes. However, when all of the other variables such as amblyopia were factored in, neither was a significant risk factor in itself as shown in the final model in Table 2.

Importantly, this cohort provides insight into the evolution of strabismus in the first year of life for infants with high-risk prethreshold ROP. For full-term infants with normal neurologic status, ocular alignment status can usually be classified by 6 months of age.[13] Infants in this study were not examined for strabismus until 6 months' corrected age, and while the presence of strabismus or the inability to assess the alignment at 6 months was predictive of strabismus at 9 months, those with strabismus at 6 months showed a 30.3% rate of spontaneous resolution by the 9-month examination. Additionally, of those with strabismus at 9 months, 42.1% had shown normal alignment at 6 months. This suggests that stability of ocular alignment is delayed, whether owing to ocular or developmental abnormalities. Study-certified pediatric ophthalmologists performed the strabismus evaluations, thus reducing the likelihood of missing small-angle strabismus or misclassifying pseudostrabismus. Phillips et al[5] reported the diagnosis of strabismus at a mean age of 8.5 months in a cohort of premature infants with birth weights less than 1500 g, and Page et al[23] noted that strabismus was seen with increasing frequency through the second year of life in a cohort of infants with birth weights less than 1251 g. Longer-term studies[2,29,30] show strabismus in up to 39% of premature infants with birth weights less than 1501 g who were followed up until 5 to 10 years of age.

The impact of abnormal developmental status on the incidence of strabismus is important, and neurodevelopmental data will be collected in the long-term follow-up of this cohort. Infants with high-risk prethreshold ROP may represent infants with a higher rate of coexisting neurologic morbidity and developmental delays, thus impacting the higher prevalence of strabismus and the instability of ocular alignment. The incidence of strabismus is about 50% for premature infants diagnosed with cerebral palsy or periventricular leukomalacia[3,22,31,32] or with evidence of grade III or IV intraventricular hemorrhage,[5] and it is increased for infants with ultrasound evidence of cerebral damage.[4]

Table 2. Multivariate Analysis to Determine Independent Variables That Increase the Odds of Developing Strabismus at 9 Months in Randomized Infants

Factor	OR (95% CI)	*P* Value
Birth weight per 100 g	0.90 (0.71-1.16)	.42
Gestational age, wk	0.96 (0.76-1.22)	.75
Race (black = 1, others = 0)	1.43 (0.61-3.34)	.41
Sex (male = 1, female = 0)	0.83 (0.43-1.62)	.59
Inborn (inborn = 1, outborn = 0)	0.35 (0.16-0.74)	.007
Single vs multiple birth (single = 1, multiple = 0)	0.56 (0.27-1.16)	.12
Anisometropia ≥2 diopters (no = 0, yes = 1)	1.13 (0.56-2.29)	.74
Fixation (both eyes normal [CSM] = 0, other = 1)	15.27 (7.02-33.21)	<.001
Visual acuity (both eyes favorable = 0, other = 1)	1.47 (0.53-4.10)	.46
Structure (both eyes favorable = 0, other = 1)	1.42 (0.46-4.42)	.54
Amblyopia (no = 0, ever diagnosed = 1)	4.22 (1.26-14.07)	.02

Abbreviations: CI, confidence interval; CSM, central, steady, and maintained; OR, odds ratio.

This article confirms that the prevalence of strabismus in the first year of life is higher for infants with high-risk prethreshold ROP compared with previously published rates for all of the preterm infants with birth weights less than 1251 g. Almost one third of these infants show strabismus by a corrected age of 9 months, and most are esotropic. There is a strong association between outborn birth status, abnormal fixation, or amblyopia and the presence of strabismus. Since a significant number of premature infants show improvement or variability in their strabismus through the first year of life, conservative management is recommended.

Submitted for Publication: August 2, 2005; final revision received December 9, 2005; accepted December 17, 2005.
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Financial Disclosure: None.

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