Published in final edited form as:
J AAPOS. 2011 December ; 15(6): 536–540. doi:10.1016/j.jaapos.2011.07.017.

Prevalence and course of strabismus through age 6 years in participants of the Early Treatment for Retinopathy of Prematurity randomized trial

Deborah K. VanderVeen, MD[a], **Don L. Bremer, MD**[b], **Rae R. Fellows, MEd**[b], **Robert J. Hardy, PhD**[c], **Daniel E. Neely, MD**[d], **Earl A. Palmer, MD**[e], **David L. Rogers, MD**[b], **Betty Tung, MS**[c], and **William V. Good, MD**[f] **on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group**[*]

[a]Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts

[b]Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio

[c]School of Public Health, University of Texas Health Science Center, Houston, Texas

[d]Department of Ophthalmology, Indiana University School of Medicine, Bloomington, Indiana

[e]Casey Eye Institute, Oregon Health & Science University, Portland, Oregon

[f]Smith-Kettlewell Eye Research Institute, San Francisco, California

Abstract

Purpose—To present strabismus data for children who participated in the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial.

Methods—The prevalence of strabismus, categorized as present or absent, was tabulated for all children with history of high-risk prethreshold retinopathy of prematurity (ROP) who participated in the ETROP randomized trial and were examined at 9 months to 6 years of age. Relationships among strabismus and demographic measures, eye characteristics, and neurodevelopmental factors were analyzed.

Results—Among the 342 children evaluated at 6 years, the prevalence of strabismus was 42.2%. Even with favorable acuity scores in both eyes the prevalence of strabismus was 25.4%, and with favorable structural outcomes in both eyes the prevalence of strabismus was 34.2%. Of children categorized as visually impaired due to either ocular or cerebral causes, 80% were strabismic at the 6-year examination. Of 103 study participants who were strabismic at 9 months, 77 (74.8%) remained so at 6 years. Most strabismus was constant at both the 9-month (62.7%) and the 6-year examination (72.3%). After multiple logistic regression analysis, risk factors for strabismus were abnormal fixation behavior in one or both eyes ($P < 0.001$), history of amblyopia ($P < 0.003$), unfavorable structural outcome in one or both eyes ($P = 0.025$), and history of anisometropia ($P = 0.04$). Strabismus surgery was performed for 53 children. By 6 years, the cumulative prevalence of strabismus was 59.4%.

Correspondence: Deborah K. VanderVeen, MD, 300 Longwood Avenue, Fegan 4, Boston MA 02115 (deborah.vanderveen@childrens.harvard.edu).

[*]A complete list of ETROP investigators is provided in e-Supplement 1, available at jaapos.org.

Conclusions—Most children with a history of high-risk prethreshold ROP develop strabismus at some time during the first 6 years of life.

Premature birth, low birth weight, and increased severity of acute-phase retinopathy of prematurity (ROP) are known risk factors for development of strabismus.[1-3] For infants with high-risk prethreshold ROP enrolled in the Early Treatment for Retinopathy of Prematurity (ETROP) randomized study, the prevalence of strabismus was 30% at 9 months' corrected age. Significant variability in the incidence of strabismus was noted between 6 and 9 months' corrected age.[4] Strong associations existed between development of strabismus and abnormal fixation, presence of amblyopia, and outborn birth status. Neurodevelopmental abnormalities, common in premature infants, are also thought to play a role in the development of strabismus.[5-8]

Here, we report strabismus data collected prospectively from 379 infants with high-risk ROP surviving to 9 months' corrected age who were enrolled in the National Eye Institute–sponsored ETROP study.[9] The prevalence and type of strabismus recorded at yearly follow-up examinations through age 6 years was tabulated. Analyses determined whether presence of strabismus correlated with demographic variables, ocular characteristics, vision scores, and/or neurodevelopmental status indicators. Strabismus surgical procedures were also tabulated.

Methods

Infants with birth weights <1251 g born between October 1, 2000, and September 30, 2002, were screened at 26 participating centers. All of the centers had the ETROP study protocol reviewed and approved by their institutional review boards (IRB) in accordance with the Health Insurance Portability and Accountability Act. Those infants who developed high-risk prethreshold ROP as determined by the RM-ROP2 model[10] were consented by parents or legal guardians for the randomized trial. If both eyes were high risk, one eye was randomized to early treatment, and the other eye was managed conventionally and treated if it reached threshold by Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) standards. If only one eye was at high risk, it was randomly assigned to early treatment or conventional management. The details of the randomization process have been published previously.[9,11]

Follow-up examinations were performed at 9 months' corrected age and yearly from ages 2 through 6. At each of these examinations, visual acuity indicators (including fixation behavior and presence or absence of nystagmus), ocular alignment, presence of amblyopia, cycloplegic refraction, and structural outcomes were recorded. Grating acuity measures were recorded at age 9 months' corrected and at 6 years, and recognition acuity scores using the ETDRS chart were recorded at 6 years. History of seizures or surgical placement of a cerebrospinal fluid shunt was recorded at the 2-year examination.

Standard clinical methods were used to assess ocular alignment in the primary position. When strabismus was observed, it was classified by the direction of deviation (esotropia, exotropia, hypertropia, or any combination thereof) and as intermittent or constant. Children were classified as unable to assess if findings were inconclusive. Surgical procedures including strabismus operations were recorded, but the magnitude of binocular deviation was not collected nor was the success of surgical outcome determined.

Normal fixation was defined as central, steady, and maintained. Grating visual acuity was measured with Teller visual acuity cards, and results were designated as favorable (1.85 cycles/degree or better) or unfavorable (<1.85 cycles/degree). ETDRS visual acuity scores at 6 years were classified as favorable (better than 20/200) or unfavorable (20/200 or worse).

All children with vision better than light perception underwent grating and ETDRS visual acuity testing at 6 years and were tested with spectacle correction for significant refractive errors.

Amblyopia was defined as abnormal fixation behavior in one eye in the absence of an unfavorable structural outcome. All amblyopic children had at least 4 weeks of treatment, usually by patching. Continued patching was advised at the discretion of the patient's ophthalmologist, based on clinical findings and response to treatment.

Clinical categories of type 1 and type 2 ROP were assigned from ROP data collected in the perinatal period.[9] Type 1 ROP is defined as zone 1 with any stage ROP with plus disease or stage 3 ROP with or without plus disease, or as zone 2 stage 2 or 3 ROP with plus disease. Type 2 ROP is defined as stage 1 or 2 ROP without plus disease in zone 1, or stage 3 ROP without plus disease in zone 2.

Statistical tests were performed using univariate analysis for each variable. Multiple logistic regression analysis including all of the variables was performed to examine the association of factors with strabismus. The *P* values for univariate analysis and for the final model are given.

Results

Of the 401 infants randomized to treatment, 379 survived to the 9 month examination, and examinations were performed on 372 infants (98.2%). Examinations were performed on 342 of 370 (94.2%) who survived to 6 years of age. A total of 341 infants were seen at both the 9-month and 6-year examinations.

Table 1 indicates the prevalence of strabismus at each study interval. The prevalence of strabismus gradually increased from 30.0% at age 9 months' corrected to 42.2% at 6 years. The cumulative prevalence of strabismus over the first 6 years was 59.4%, as some patients showed strabismus at one data point and not at others.

For both outcome stages, the rate of strabismus by demographic variables and ROP type is given in Table 2. At 9 months the prevalence of strabismus was 44.4% in outborn infants and 26.4% in inborn babies ($P = 0.003$), but this difference was not found at 6 years (47.0% vs 41.0%, $P = 0.38$). Prevalence of strabismus for infants with type 1 ROP was 43.9% at 6 years of age. There was no significant difference in rates of strabismus based on type 1 versus type 2 classification ($P = 0.44$).

Table 3 shows strabismus rates in the 341 children who were seen for both the 9-month and 6-year examinations. Of the 103 infants who were strabismic at the 9-month examination, 77 (74.8%) remained so at 6 years and 21 (20.4%) showed normal alignment at the 6-year examination. Of these 21, only 5 had undergone strabismus surgery. Of the 235 infants with normal alignment at 9 months, 63 (26.8%) were strabismic at 6 years.

Esotropia was found in 79 of 110 of the infants (71.8%) with strabismus at the 9 month exam, compared to 79 of 141 (56.0%) at the 6-year examination. Exotropia was found in 29 of 110 of infants (26.4%) at 9 months, and 37 of 141 (26.2%) were exotropic at the 6-year examination. More children showed constant strabismus at the 6-year examination (72.3%) compared to the 9-month examination (62.7%). Only 2 infants showed more than one direction (any combination of esodeviation, exodeviation, hyperdeviation) of strabismus at 9 months, but there were 25 such children at 6 years. One child had Duane syndrome.

Overall, strabismus operations were performed on 53 children. The majority (42/53, 79%) remained strabismic (diagnosed as present or absent) at the 6-year examination. Of the 21 infants with strabismus at 9 months that resolved by the 6-year examination, only 5 (24%) had surgery in the interval.

With regard to ETROP visual and structural outcome measures, univariate analysis showed strabismus rates at 6 years were significantly higher when there was (1) an unfavorable structural outcome in one or both eyes (87.0%, vs 34.2% with favorable structural outcome in both eyes; $P < 0.001$), (2) an abnormal fixation in one or both eyes (71.1%, vs 16.0 % with normal fixation in both eyes; $P < 0.001$), or (3) an unfavorable visual acuity in one or both eyes (67.3%, vs 25.4% with favorable vision in both eyes; $P < 0.001$). Rates of strabismus were also higher if amblyopia was ever diagnosed (60.2%, vs 32.4% if never diagnosed; $P < 0.001$), if anisometropia >2 D was ever present (45.8%, vs 31.7% never anisometropic ≥2 D; $P = 0.017$), or if there was a history of seizures or cerebrospinal fluid shunt placement by 2 years (60.5% vs 39.5%, $P = 0.046$). For children considered visually impaired by the examining physician, whether due to ROP or cerebral causes, 80% were strabismic at the 6-year examination.

Using multiple logistic regression analysis (Table 4), the significant factors associated with strabismus at 6 years were abnormal fixation behavior, history of amblyopia, unfavorable structural outcome, and history of anisometropia ≥2 D. Abnormal fixation behavior in one or both eyes was associated with a 5.28 times greater risk of strabismus, and unfavorable structural outcome in one or both eyes was associated with a 4.93 times greater risk of strabismus. Less influence on risk of strabismus was associated with history of amblyopia (2.91 times greater risk) and history of anisometropia (0.47 times greater risk).

Discussion

This is a large, prospective study of more than 400 infants with high-risk prethreshold ROP examined longitudinally from birth to 6 years of age. It demonstrates that the prevalence of strabismus among ETROP survivors continues to rise through 6 years of age, to 42.4%, with almost 60% of children reported strabismic on at least one data point during the first 6 years of life. Even among the subset of children with favorable structural and visual outcomes in both eyes, the prevalence of strabismus at 6 years is 26%. Such a high rate is not unexpected, since it has been shown that strabismus rates are higher in preterm infants, particularly in those with more severe acute-phase ROP.[3-5,8,11]

Many different factors other than acute phase ROP have been associated with strabismus. In this study, multiple regression analysis found a positive association of strabismus with abnormal fixation in one or both eyes, any history of amblyopia, or abnormal structure in one or both eyes at the six year examination ($P < 0.05$ level). All of these factors have been previously associated with strabismus at one year of age in infants with a history of prematurity.[4,12] While eyes in this cohort were randomized to different timing of treatment, which could theoretically affect refractive development and induce anisometropia, previous reports have shown no significant differences between eyes managed with early treatment and those managed conventionally with regard to prevalence of myopia at 9 months or 3 years[13,14] or astigmatism at 3 years.[15] In addition, a history of anisometropia >2 D was positively associated with strabismus at the 6-year examination by univariate analysis (1.76 odds ratio, $P = 0.017$) but was negatively associated with strabismus in multivariate analysis, suggesting that this measure of anisometropia is probably not a clinically important cause of strabismus in this population. In the final analysis, evaluation of fixation behavior showed a stronger association with strabismus risk than recognition acuity measures. This is most likely due to inclusion of more patients that could be evaluated by fixation behavior

alone, compared to the subset of patients who were able to cooperate for ETDRS visual acuity measures.

Previously, we showed that amblyopia at 1 year of age was associated with strabismus at 1 year of age, and this study shows that amblyopia reported at any time before 6 years of age is a risk factor for strabismus at the 6-year examination. We did not evaluate the temporal relationship between diagnosis of amblyopia and onset of strabismus. Additionally, we could not demonstrate whether the diagnosis of amblyopia contributed to the development of strabismus, or the presence of strabismus contributed to the development of amblyopia.

Neurologic abnormalities have been shown to be associated with increased strabismus rates in larger populations with less severe ROP.[2,5-7] In the multivariate analysis in this study, history of shunted hydrocephalus or seizure disorder at 2 years of age was not found to carry a significant risk for strabismus at 6 years. The presence of neurologic or neurodevelopmental abnormalities was not assessed after 2 years of age.

Most children who were strabismic at the 9-month examination remained so; however, some of the children who were strabismic in infancy showed normal alignment at the 6 year examination even without surgery. Additionally, constant deviations were more common over time. Only 14.0% of the cohort (53/379) eventually had at least one strabismus procedure, which is slightly higher than the rate of strabismus surgery performed by age 5.5 years for all children randomized in the Cryotherapy for Retinopathy of Prematurity randomized trial (10%).[16] In the majority of cases (79%), children remained strabismic even after surgery, but we did not attempt to define or determine surgical success. It is likely that potential for binocular vision is relatively low in this population, due to factors attributable to ocular or visual function abnormalities.

In conclusion, strabismus is a common finding in children with high-risk prethreshold or Type 1 ROP, showing an increasing prevalence through 6 years of age. Most children with strabismus show constant misalignment by 6 years, irrespective of whether surgical correction was performed, and delayed stabilization of alignment is common. Caution should be exercised when considering expectations for normal alignment or binocular function in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. O'Connor AR, Stephenson T, Johnson A, et al. Strabismus in children of birth weight less than 1701 grams. Arch Ophthal. 2002; 12:767–73.
2. Torp-Pedersen T, Boyd HA, Poulsen G, et al. Perinatal risk factors for strabismus. Int J Epidemiol. 2010; 39:1229–39. [PubMed: 20525734]
3. Cats BP, Tan KEWP. Prematures with and without regressed retinopathy of prematurity: Comparison of long-term (6-10 years) ophthalmological morbidity. J Pediatr Ophthalmol Strabismus. 1989; 26:271–5. [PubMed: 2621545]
4. VanderVeen DK, Coats DK, Dobson V, et al. Early Treatment for Retinopathy of Prematurity Cooperative Group. Prevalence and course of strabismus in the first year of life for infants with prethreshold retinopathy of prematurity. Arch Ophthalmol. 2006; 124:766–3. [PubMed: 16769828]
5. Pennefather PM, Clarke MP, Strong NP, et al. Risk factors for strabismus in children born before 32 weeks' gestation. Br J Ophthalmol. 1999; 83:514–18. [PubMed: 10216046]
6. Hungerford J, Stewart A, Hope P. Ocular sequelae of preterm birth and their relation to ultrasound evidence of cerebral damage. Br J Ophthalmol. 1986; 70:463–8. [PubMed: 3521718]

7. Philips J, Christiansen SP, Ware G, et al. Ocular morbidity in very low birthweight infants with intraventricular hemorrhage. Am J Ophthalmol. 1997; 123:218–23. [PubMed: 9186128]
8. Sahni J, Subhedar NV, Clark D. Treated threshold stage 3 versus spontaneously regressed subthreshold stage 3 retinopathy of prematurity: A study of motility, refractive, and anatomical outcomes at 6 months and 36 months. Br J Ophthalmol. 2005; 89:154–9. [PubMed: 15665344]
9. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the Early Treatment for Retinopathy of Prematurity randomized trial. Arch Ophthalmol. 2003; 121:1684–96. [PubMed: 14662586]
10. Hardy RJ, Palmer EA, et al. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Risk analysis of prethreshold retinopathy of prematurity. Arch Ophthalmol. 2003; 121:1697–1701. [PubMed: 14662587]
11. Early Treatment for Retinopathy of Prematurity Cooperative Group. Multicenter trial of early treatment for retinopathy of prematurity: Study design. Control Clin Trials. 2004; 25:311–25. [PubMed: 15157731]
12. Bremer DL, Palmer EA, Fellows RR, et al. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Strabismus in premature infants in the first year of life. Arch Ophthalmol. 1998; 116:329–33. [PubMed: 9514486]
13. Davitt BV, Dobson V, Good WV, et al. Early Treatment for Retinopathy of Prematurity Cooperative Group. Prevalence of myopia at 9 months in infants with high-risk prethreshold retinopathy of prematurity. Ophthalmol. 2005; 112:1564–8.
14. Quinn GE, Dobson V, Davitt BV, et al. Early Treatment for Retinopathy of Prematurity Cooperative Group. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity Study: Findings to 3 years of age. Ophthalmol. 2008; 115:1058–64.e1.
15. Davitt BV, Dobson V, Quinn GE, et al. Early Treatment for Retinopathy of Prematurity Cooperative Group. Astigmatism in the Early Treatment for Retinopathy of Prematurity Study: Findings to 3 years of age. Ophthalmol. 2009; 116:332–9.
16. Repka MX, Summers CG, Palmer EA, et al. Cryotherapy for Retinopathy of Prematurity Cooperative Group. The incidence of ophthalmologic interventions in children with birth weights less than 1251 grams. Ophthalmology. 1998; 105:1621–7. [PubMed: 9754167]

Table 1

Prevalence of strabismus at 9 months to 6 years examinations for patients in the randomized ETROP study

	Total	No. strabismus	No. normal	No. UA	% Strabismus
9 months	372	110	257	5	30.0
2 years	339	112	220	7	33.7
3 years	326	123	196	7	38.6
4 years	319	121	191	7	38.8
5 years	313	129	179	5	41.9
6 years	342	141	193	8	42.2

UA, unable to access: infants deemed unable to assess and not included in the percentage calculations.

J AAPOS. Author manuscript; available in PMC 2012 December 1.

Table 2

Percentage of strabismus by demographic variables and ROP type at 9 months and 6 years

		9 months				6 years			
		Normal	Strabismus	Strabismus %	UA	Normal	Strabismus	Strabismus %	UA
Birth weight (grams)	<750	167	73	30.4	3	126	94	42.7	5
	750-999	75	36	32.4	2	59	40	40.4	3
	≥1000	15	1	6.3	0	8	7	46.7	0
GA (weeks)	<28	249	105	29.7	5	189	134	41.5	8
	28-31	8	5	38.5	0	4	7	63.6	0
	>31	0	0	---	0	0	0	---	0
Race	White	159	75	32.1	2	116	98	45.8	6
	Black	46	19	29.2	2	35	26	42.6	0
	Other	52	16	23.5	1	42	17	28.8	2
Sex	Male	134	61	31.3	4	100	80	44.4	6
	Female	123	49	8.5	1	93	61	39.6	2
Born in hospital	Inborn	217	78	26.4	4	158	110	41.0	6
	Outborn	40	32	44.4	1	35	31	47.0	2
Multiple births	Yes	73	33	31.1	1	64	37	36.6	2
	No	184	77	29.5	4	129	104	44.6	6
ROP type	Type 1	186	83	30.9	3	137	107	43.9	8
	Type 2	64	25	28.1	2	50	32	39.0	0

GA, gestational age; *ROP*, retinopathy of prematurity; *UA*, unable to assess: infants deemed unable to assess and not included in the percentage calculations.

Table 3

Presence of strabismus in patients seen at both 9-month and 6-year examinations

	6-year examinations		
9-month examination	**Normal**	**Strabismus**	**UA***
Normal	171	63	1
Strabismus	21	77	5
Unable to grade	1	0	2

* *UA*, unable to access: infants deemed unable to assess and not included in the percentage calculations.

Table 4

Univariate and multivariate analysis to determine independent variables that increase the odds of developing strabismus at 6 years

Factors	Univariate analysis	Multivariate analysis	
	P value	OR [CI]	*P* Value
Birthweight (100g)	0.73	1.02 [0.82-1.28]	0.83
Gestational age (weeks)	0.42	0.96 [0.75-1.22]	0.73
Race (black,1; other, 0)	0.94	0.93 [0.43-2.02]	0.86
Sex (male,1; female, 0)	0.37	1.10 [0.59-2.03]	0.77
Inborn (inborn, 1; outborn, 0)	0.38	0.84 [0.40-1.77]	0.65
Multiple births (single,1; multiple, 0)	0.18	1.11 [0.58-2.10]	0.76
Anisometropia ≥2 D (no, 0; yes, 1)	0.017	0.47 [0.23-0.97]	0.04
Fixation (both eyes normal, 0; others, 1)	<0.001	5.28 [2.68-10.42]	<0.001
ETDRS acuity (both eyes favorable, 0; others, 1)	<0.001	1.82 [0.89-3.70]	0.10
Ocular structure (both eyes favorable, 0; others, 1)	<0.001	4.93 [1.23-19.82]	0.025
Amblyopia (no, 0; ever diagnosed, 1)	<0.001	2.91 [1.45-5.85]	0.003
Seizure/ shunt at 2-year examination (no, 0; ever diagnosed, 1)	0.046	1.02 [0.42-2.47]	0.96

CI, confidence interval; *OR*, odds ratio.