Treatment of Bilateral Refractive Amblyopia in Children Three to Less Than 10 Years of Age

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• PURPOSE: To determine the amount and time course of binocular visual acuity improvement during treatment of bilateral refractive amblyopia in children three to less than 10 years of age.

• DESIGN: Prospective, multicenter, noncomparative intervention.

• METHODS: One hundred and thirteen children (mean age, 5.1 years) with previously untreated bilateral refractive amblyopia were enrolled at 27 community- and university-based sites and were provided with optimal spectacle correction. Bilateral refractive amblyopia was defined as 20/40 to 20/400 best-corrected binocular visual acuity in the presence of 4.00 diopters (D) or more of hypermetropia by spherical equivalent, 2.00 D or more of astigmatism, or both in each eye. Best-corrected binocular and monocular visual acuities were measured at baseline and at five, 13, 26, and 52 weeks. The primary study outcome was binocular acuity at one year.

• RESULTS: Mean binocular visual acuity improved from 0.50 logarithm of the minimum angle of resolution (logMAR) units (20/63) at baseline to 0.11 logMAR units (20/25) at one year (mean improvement, 3.9 lines; 95% confidence interval [CI], 3.5 to 4.2). Mean improvement at one year for the 84 children with baseline binocular acuity of 20/40 to 20/80 was 3.4 lines (95% CI, 3.2 to 3.7) and for the 16 children with baseline binocular acuity of 20/100 to 20/320 was 6.3 lines (95% CI, 5.1 to 7.5). The cumulative probability of binocular visual acuity of 20/25 or better was 21% at five weeks, 46% at 13 weeks, 59% at 26 weeks, and 74% at 52 weeks.

• CONCLUSIONS: Treatment of bilateral refractive amblyopia with spectacle correction improves binocular visual acuity in children three to less than 10 years of age, with most improving to 20/25 or better within one year. (Am J Ophthalmol 2007;144:487–496. © 2007 by Elsevier Inc. All rights reserved.)

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BILATERAL REFRACTIVE AMBLYOPIA CAN DEVELOP IN children with large amounts of uncorrected hypermetropia, astigmatism, or both in each eye. Treatment consists of prescribing the appropriate refractive correction with the possible addition of occlusion or pharmacologic penalization if asymmetric visual acuity is present after correction is provided. The prevalence of bilateral amblyopia at the time of entry into school was estimated in one study to be 0.5% (four of 830 children).[1] The presumed mechanism of bilateral refractive amblyopia is pattern vision deprivation. Abnormal binocular interaction with suppression also may contribute in those cases with concomitant strabismus.[2] There are few published studies of treatment for bilateral amblyopia.[3–9] Most have been limited by small numbers of subjects and short follow-up times. To address these limitations, we designed a prospective cohort study to determine the amount and time course of binocular visual acuity improvement during usual treatment of previously untreated bilateral refractive amblyopia.

METHODS

THE PEDIATRIC EYE DISEASE INVESTIGATOR GROUP CONducted this study at 27 community- and university-based clinical sites, and it was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health. The parent or guardian of each study participant gave written informed consent. Some IRBs required that children older than a certain age give their assent for participation; assent was given by each child for whom the institutional review board (IRB) required it. The major aspects of the protocol are summarized herein. The complete protocol is available at http://public.pedig.jaeb.org.

The major eligibility criteria included age three to less than 11 years; binocular visual acuity of 20/40 to 20/400 in optimal refractive correction; cycloplegic refractive error in each eye of 4.00 diopters (D) or more of hypermetropia (spherical equivalent), 2.00 D or more of astigmatism (including some eyes with myopic astigmatism), or both; no myopia of more than −6.00 D of spherical power in plus cylinder form; no previous treatment for amblyopia except one month or less of spectacle wear terminating

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three months or more before enrollment; no amblyopia treatment planned other than spectacles; and no cause for reduced visual acuity suspected other than bilateral refractive amblyopia.

At a screening visit, visual acuity was measured using trial frames or a phoropter with correction from a cycloplegic refraction (using cyclopentolate 1%). The method for determining adequacy of cycloplegia was at the investigator's discretion. Children who were potentially eligible were prescribed spectacles in which anisometropia, astigmatism, and myopia were fully corrected and in which hypermetropia was either fully corrected or undercorrected symmetrically by no more than 1.50 D in both eyes. There was no untreated control group.

Spectacles were worn, for the first time, for 10 to 30 minutes before visual acuity was measured at the baseline visit. A study-certified vision tester measured visual acuity first binocularly, then for each eye separately. Children three to six years of age were tested using the Amblyopia Treatment Study (ATS) single-surround HOTV visual acuity testing protocol, which yields a line score (Snellen score),[10] whereas children age 7 to 10 years were tested with the electronic Early Treatment of Diabetic Retinopathy Study (e-ETDRS) testing protocol, which yields a letter score.[11] If either eye's monocular acuity tested worse at baseline than at the screening visit, acuity was to be retested. In children whose prescribed spectacles contained hypermetropic correction, because of the possibility that the reduced acuity was the result of incomplete relaxation of accommodation, the retesting was to be completed using a −1.00 D lens over the spectacles. Stereopsis was measured using the Randot Preschool Stereoacuity Test (Stereo Optical Company, Chicago, Illinois, USA), and ocular alignment was assessed using the simultaneous prism and cover test.

Protocol-specified follow-up visits were conducted at five, 13, 26, and 52 weeks after the baseline examination. If monocular acuity was 20/25 or better in both eyes at the five-week or 13-week visit, then subsequent visits before the one-year examination were skipped. At each follow-up visit, visual acuity was measured with spectacle correction first binocularly and then monocularly for the right eye and then the left eye. At the one-year examination, additional testing included the Randot Preschool Stereoacuity Test and a refraction (manifest or cycloplegic). A refraction also was performed any time the investigator suspected that refractive error was not optimally corrected. Whenever a significant change in refractive error was detected (as defined in the protocol), monocular and binocular acuities were retested using the new refractive correction in a trial frame.

Spectacle correction changes during follow-up were at the investigator's discretion. Additional amblyopia treatment with patching, atropine, or both also was initiated at the investigator's discretion; however, it was suggested that treatment be started only after monocular visual acuity had stopped improving in each eye.

• **STATISTICAL METHODS:** Visual acuity data for patients younger than seven years were combined with visual acuity data from patients 7 years of age or older by converting to a common logarithm of the minimum angle of resolution (logMAR) scale both the HOTV line scores from the younger patients and the e-ETDRS letter scores from the older patients. A change of 0.1 logMAR units was considered to be a one-line change in acuity (equivalent to a five-letter change using the e-ETDRS testing method).

The primary study outcome was binocular visual acuity at one year. Mean lines of binocular acuity improvement from baseline to one year were computed along with a 95% confidence interval (CI). The one-year cumulative probability of reaching a binocular acuity of 20/25 or better and a 95% CI were computed using the Kaplan-Meier product-limit method.

The associations of baseline characteristics with lines of visual acuity improvement at one year and with the proportion of children achieving binocular acuity 20/25 or better during follow-up were evaluated using linear regression and proportional hazards regression, respectively. All regression models included baseline binocular visual acuity as a covariate. The average of the two eyes was used to assess spherical equivalent and astigmatism.

The associations of refractive error type (hypermetropia vs astigmatism) with lines of visual acuity improvement at one year and with the proportion achieving binocular acuity 20/25 or better during follow-up were evaluated using linear regression and proportional hazards regression, respectively, in a subset of children who had either significant hypermetropia only or significant astigmatism only. Baseline binocular visual acuity was included in the models as a covariate. Among children who at baseline had significant hypermetropia but no significant astigmatism, the association between baseline hypermetropia and baseline binocular acuity was evaluated using linear regression. The association of binocular acuity improvement at one year with stereoacuity improvement at one year was assessed using the Pearson correlation. Mean lines of monocular acuity improvement from baseline to one year and a 95% CI were computed using data from both eyes of each child and using generalized estimating equations to account for the within-subject correlation. All reported *P* values are two tailed. Analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, North Carolina, USA).

RESULTS

• **BASELINE CHARACTERISTICS:** Between August 11, 2004 and June 29, 2005, 113 children with a mean age of 5.1 ± 1.3 years were enrolled into this study at 27 clinical sites. Mean baseline binocular visual acuity was 0.50 logMAR units (Snellen equivalent, approximately 20/63).

TABLE 1. Baseline Characteristics of Study Cohort of Patients Aged 3 to Less than 10 Years with Previously Untreated Bilateral Refractive Amblyopia (n = 113)

Characteristics	n (%)
Female	50 (44)
Race/ethnicity	
White	70 (62)
Black	16 (14)
Hispanic or Latino	21 (19)
Other	6 (5)
Age (yrs)	
Mean (SD)	5.1 (1.3)
Range	3.0 to 9.2
3 to <4	24 (21)
4 to <5	30 (27)
5 to <6	38 (34)
6 to <7	11 (10)
7 to <8	5 (4)
8 to <9	4 (4)
9 to <10	1 (1)
10 to <11	0 (0)
Binocular visual acuity	
Mean logMAR [Snellen equivalent], (SD)	0.50 [20/63] (0.18)
Range [Snellen equivalent]	0.30 to 1.20 [20/40 to 20/320]
20/40 to 20/50	56 (50)
20/60 to 20/80	38 (34)
20/100 to 20/160	16 (14)
20/200 to 20/320	3 (3)
Worse than 20/320	0 (0)
Interocular acuity difference (no. lines)	
Mean (SD)	1.1 (1.6)
Range	0.0 to 8.0
0 to <1	50 (44)
1 to <2	40 (35)
2 to <3 lines	11 (10)
≥3	12 (11)
Type of refractive amblyopia in both eyes*	
Significant hypermetropia only	40 (35)
Significant astigmatism only	46 (41)
Both significant hypermetropia and astigmatism	18 (16)
Mixed†	9 (8)
Spherical equivalent (D)‡	
Mean (SD), spherical equivalent	4.7 (3.1)
Range, spherical equivalent	−2.75 to 11.00
<0.00	6 (5)
0.00 to <4.00	41 (36)
4.00 to <7.00	36 (32)
≥7.00	30 (27)
Astigmatism (D)‡	
Mean (SD), cylinder	2.4 (1.5)
Range, cylinder	0.0 to 6.50
<2.00	43 (38)
2.00D to <4.00	54 (48)
4.00D to <6.00	14 (12)
≥6.00	2 (2)

(*Continued*)

TABLE 1. (*Continued*)

Characteristics	n (%)
Anisometropia (D)	
Mean (SD), spherical equivalent	0.4 (0.4)
Range, spherical equivalent	0.00 to 2.50
0.00	25 (22)
>0.00 to <0.50	40 (35)
0.50 to <1.00	37 (33)
1.00 to <1.50	8 (7)
≥1.50	3 (3)
Hypermetropic spectacle correction prescribed[§]	
Fully corrected	20 (19)
Undercorrected≤0.50 D	6 (6)
Undercorrected >0.50 to 1.00 D	49 (46)
Undercorrected >1.00 to 1.50 D	31 (29)
Stereoacuity, seconds of arc[‖]	
40	4 (4)
60	5 (5)
100	5 (5)
200	5 (5)
400	10 (9)
800	15 (14)
None detected (>800)	66 (60)
Strabismus present[¶]	15 (13)

D = diopters; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

*Significant hypermetropia refers to spherical equivalent ≥4.00 D; significant astigmatism refers to cylinder ≥2.00 D.

[†]Seven children had significant hypermetropia and significant astigmatism in one eye and significant hypermetropia and no significant astigmatism in the other eye, and two children had significant hypermetropia and significant astigmatism in one eye and significant astigmatism and no significant hypermetropia in the other eye.

[‡]Refers to the average amount between the two eyes.

[§]Excluded are seven children who had no hypermetropia: six had myopia and one had neither hypermetropia or myopia. Per protocol, hypermetropic spectacle correction could be either fully corrected or undercorrected symmetrically in both eyes up to 1.50 D.

[‖]Three children were unable to perform stereoacuity testing.

[¶]Strabismus refers to the presence of a horizontal tropia at distance or at near, or a history of strabismus or strabismus surgery.

Twenty-three children (20%) had 2 lines or more of interocular difference (IOD) in visual acuity. Additional baseline characteristics are included in Table 1.

Among 40 children with significant bilateral hypermetropia only (hypermetropia of 4.00 D or more by spherical equivalent and astigmatism of less than 2.00 D), higher levels of hypermetropia were associated with worse baseline binocular visual acuity ($P \leq .001$). Mean baseline binocular acuity was 0.46 logMAR units (Snellen equivalent, approximately 20/63) in the 17 children with 4.00 D to less than 7.00 D of hypermetropia and 0.67 logMAR units (Snellen equivalent, approximately 20/100) in the 23 children with 7.00 D or more of hypermetropia. Mean baseline binocular acuity was worse among the 40 children with significant bilateral hypermetropia only, compared with the 46 children with significant bilateral astigmatism only (mean acuity, 0.58 vs. 0.44 logMAR units, respectively; $P \leq .001$).

At the baseline visit, there were eight children (7%) whose monocular acuity in one or both eyes tested 2 lines or more lines worse from the enrollment acuity and whose spectacles contained hyperopic correction. By protocol, these children should have had their acuity retested using a −1.00 D lens, but none completed this retesting. Four of these children (50%) had a baseline binocular acuity which was 2 lines or more worse than the better of their enrollment monocular acuities.

• **STUDY COMPLETION:** The study was completed by 101 (89%) of the 113 children (Figure 1). Children not completing the study were similar to children completing the study in terms of baseline characteristics including age (4.5 vs 5.1 years; $P = .09$), baseline binocular visual acuity (mean, 0.53 vs 0.49 logMAR units; $P = .70$), interocular acuity difference (1.3 vs 1.1 lines; $P = .68$), spherical equivalent (5.3 vs 4.7 D; $P = .52$), and astigmatism (2.0 vs 2.4. D; $P = .35$).

• **TREATMENT DURING FOLLOW-UP:** Of the 109 children entering the study and completing at least one

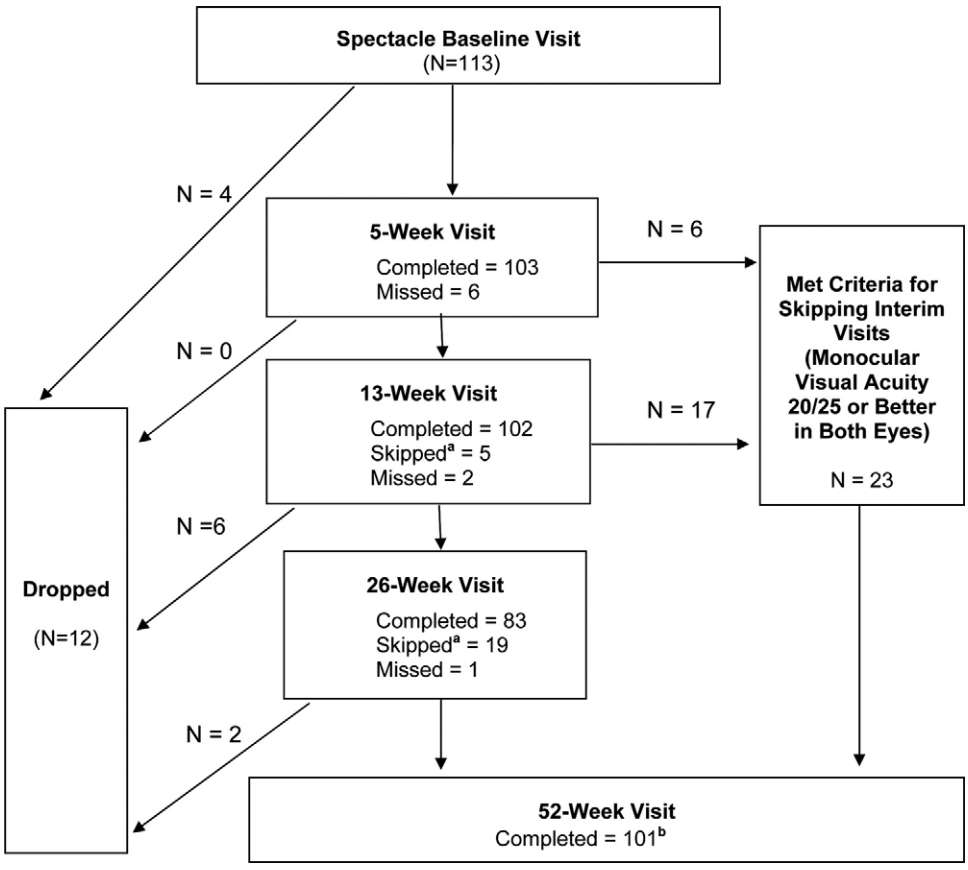

FIGURE 1. Flow diagram showing one-year follow-up for patients with bilateral refractive amblyopia (n = 113). [a]Skipped indicates visit was skipped because the patient had monocular visual acuity of 20/25 or better in both eyes at a previous visit. Some patients skipped both the 13-week and the 26-week visit. [b]One patient who completed the 52-week visit did not undergo binocular acuity measurement.

follow-up visit, 96 (88%) were treated with spectacles alone during follow-up and 13 (12%) received additional amblyopia treatment (patching for 12 children and both patching and atropine for one child). Compliance with spectacle wear was reported as excellent (spectacles worn 75% to 100% of the waking hours) at every completed visit for 74 children (68%).

• **BINOCULAR VISUAL ACUITY IMPROVEMENT:** Binocular visual acuity (mean at baseline, 0.50 logMAR units; Snellen equivalent, 20/63) improved by an average of 2.3 lines (95% CI, 2.0 to 2.6) to a mean of 0.26 logMAR units (Snellen equivalent, 20/40) after five weeks and by an average of 3.9 lines (95% CI, 3.5 to 4.2) to a mean of 0.11 logMAR units (Snellen equivalent, 20/25) at one year (Table 2). Mean improvement at one year for the 84 children with baseline binocular visual acuity of 20/40 to 20/80 was 3.4 lines (95% CI, 3.2 to 3.7) and for the 16 with baseline binocular visual acuity of 20/100 to 20/400 was 6.3 lines (95% CI, 5.1 to 7.5). Overall, the cumulative probability of reaching binocular acuity of 20/25 or better was 21% at five weeks, 46% at 13 weeks, 59% at 26 weeks, and 74% (95% CI, 66% to 82%) at one year (Figure 2). All 15 children who first achieved 20/25 or better binocular acuity at the one-year visit had completed the three prior follow-up visits.

We evaluated the effect of a single outlier on analyses related to mean improvement in binocular acuity—a 9-year-old child with astigmatism whose binocular acuity improved 12.8 lines at one year. In all analyses, excluding data from this outlier did not substantively change results except where noted.

• **FACTORS PREDICTIVE OF BINOCULAR ACUITY IMPROVEMENT:** Table 3 shows the binocular acuity outcome data stratified by baseline demographic and clinical characteristics. The number of lines of binocular acuity improvement was more with worse baseline binocular acuity ($P < .001$). The cumulative probability of achieving 20/25 or better binocular acuity during follow-up was greater in children with better baseline binocular acuity ($P < .001$).

Among children who completed the study, the 34 children with significant bilateral hypermetropia only seemed to have had greater binocular acuity improvement than the 44 children with significant bilateral astigmatism only (estimated difference between groups adjusted for baseline acuity, 0.06 logMAR units; $P = .04$); however, this association no longer existed when data were analyzed excluding the single outlier who had 12.8 lines of improvement (estimated difference between groups adjusted for baseline acuity, 0.04 logMAR units; $P = .18$). Children with significant bilateral hypermetropia only were similar to children with significant bilateral astigmatism only in the cumulative probability of reaching 20/25 or better binocular acuity over one year (69% vs 86%; $P = .13$).

TABLE 2. Binocular Visual Acuity Outcomes during One Year of Spectacle Wear in Patients 3 to Less than 10 Years of Age with Previously Untreated Bilateral Refractive Amblyopia (n = 113)*

Visual Acuity Outcome, No. Lines	All Patients (n = 113), No. (%)	Baseline Binocular Acuity	
		20/40 to 20/80 (n = 94), No. (%)	20/100 to 20/320 (n = 19), No. (%)
Change in binocular acuity from baseline to one year			
Mean (SD)	3.9 (1.8)	3.4 (1.3)	6.3 (2.3)
Range	0.0 to 12.8	0.0 to 7.0	3.0 to 12.8
0	1 (1)	1 (1)	0 (0)
1	5 (5)	5 (6)	0 (0)
2	11 (11)	11 (13)	0 (0)
3	31 (31)	30 (36)	1 (6)
4	25 (25)	22 (26)	3 (19)
5	13 (13)	12 (14)	1 (6)
6	6 (6)	2 (2)	4 (25)
7	5 (5)	1 (1)	4 (25)
8	2 (2)	0 (0)	2 (13)
>8	1 (1)	0 (0)	1 (6)
Binocular acuity at one year			
Mean logMAR [Snellen equivalent], (SD) logMAR	0.11 [20/25], (0.13)	0.09 [20/25], (0.12)	0.18 [20/32], (0.16)
Range, logMAR [Snellen equivalent]	−0.10 to 0.50 [20/16 to 20/63]	−0.10 to 0.40 [20/16 to 20/50]	−0.08 to 0.50 [20/16 to 20/63]
20/16	8 (8)	7 (8)	1 (1)
20/20	28 (28)	26 (31)	2 (13)
20/25	33 (33)	28 (33)	5 (31)
20/32	18 (18)	15 (18)	3 (19)
20/40	8 (8)	6 (7)	2 (13)
20/50	4 (4)	2 (2)	2 (13)
20/63	1 (1)	0 (0)	1 (6)
Worse than 20/63	0 (0)	0 (0)	0 (0)
Binocular acuity 20/25 or better at any follow-up visit	79 (74)†	70 (78)†	9 (55)†

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

*Binocular acuity data at one year are missing for 13 children: 10 children with baseline binocular acuity of 20/40 to 20/80 and three children with baseline binocular acuity of 20/100 to 20/320. Therefore, the effective numbers for change in binocular acuity and for binocular acuity at one year are both 100 children overall.

†Percentages are cumulative probabilities were derived using the Kaplan-Meier product-limit method.

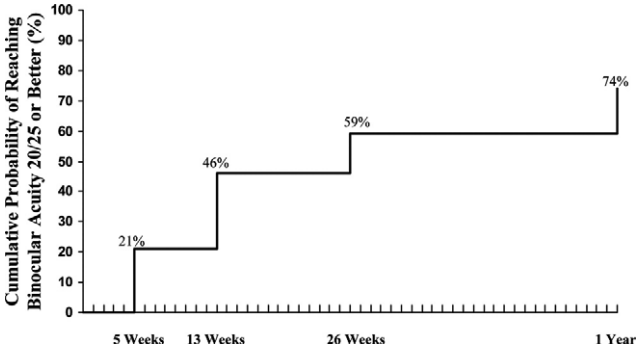

FIGURE 2. Graph showing the cumulative probability of binocular visual acuity of 20/25 or better during follow-up of patients with bilateral refractive amblyopia (n = 113).

• **BINOCULAR VISUAL ACUITY IMPROVEMENT IN CHILDREN ALSO TREATED WITH PATCHING, ATROPINE, OR BOTH:** Among the 13 children who were treated with spectacles and either patching, atropine, or both, binocular visual acuity (mean at baseline, 0.53 logMAR units; Snellen equivalent, 20/63) improved by an average of 3.3 lines (95% CI, 2.1 to 4.4) to a mean of 0.22 (Snellen equivalent, 20/32) at one year. The cumulative probability of reaching binocular acuity 20/25 or better was 49% (95% CI, 25% to 78%) at one year.

• **MONOCULAR ACUITY IMPROVEMENT:** Monocular visual acuity (mean at baseline, 0.57 logMAR units; Snellen equivalent, 20/80) improved by an average of 2.3 lines (95% CI, 2.1 to 2.6) to a mean of 0.33 logMAR units (Snellen equivalent, 20/40) after five weeks and by an

TABLE 3. Binocular Acuity Outcomes during One Year of Spectacle Wear in Patients 3 to Less than 10 Years of Age with Previously Untreated Bilateral Refractive Amblyopia Stratified by Baseline Characteristics (n = 113)

Characteristics	Binocular Acuity					
	No. of Lines of Improvement at One Year*			20/25 or Better at Any Follow-up Visit†		
	n	Mean	*P* value	n	n (%)	*P* value
Gender			.28			.09
Female	42	3.9		50	39 (84)	
Male	58	3.9		63	40 (67)	
Race/ethnicity			.11			.93
White	62	3.9		70	47 (71)	
Nonwhite	38	3.9		43	31 (79)	
Age (yrs)			.17			.71
3 to <4	19	3.7		24	16 (75)	
4 to <5	26	4.0		30	19 (66)	
5 to <6	35	4.0		38	28 (79)	
6 to <7	10	3.1		11	9 (82)	
7 to <10	10	4.3		10	7 (70)	
Strabismus			.84			.46
Present	12	3.7		15	12 (91)	
Absent	88	3.9		98	67 (72)	
Hypermetropia,‡ spherical equivalent (D)			.94			.75
4.00 to <7.00	29	3.3		36	23 (71)	
≥7.00	27	4.7		30	17 (60)	
Astigmatism (D)§			.46			.78
2.00 to <4.00	47	3.7		54	38 (76)	
4.00 to <6.00	14	3.5		14	10 (71)	
≥6.00	2	5.3		2	2 (100)	
Anisometropia (D)			.39			.56
0.00	21	4.6		25	17 (76)	
>0.00 to <0.50	35	3.7		40	24 (62)	
0.50 to <1.00	33	3.8		37	28 (80)	
1.00 to <1.50	8	3.9		8	7 (88)	
≥1.50	3	2.2		3	3 (100)	
Binocular visual acuity			<.001			<.001
20/40 to <20/50	49	3.1		56	47 (89)	
20/60 to 20/80	35	3.9		38	23 (63)	
20/100 to 20/320	16	6.3		19	9 (55)	
Interocular acuity difference (no. lines)						
0 to <1	44	4.1	.05	50	35 (74)	.84
1 to <2	36	3.8		40	27 (72)	
2 to 3	9	3.9		11	10 (91)	
≥3	11	3.3		12	7 (64)	

(*Continued on next page*)

average of 3.9 lines (95% CI, 3.7 to 4.2) to a mean of 0.17 logMAR units (Snellen equivalent, 20/32) at one year. At one year, 13 children (13%) had monocular acuity 20/40 or worse in both eyes and 34 children (34%) had monocular acuity 20/40 or worse in one eye.

• **CHANGE IN IOD:** Of the 23 children who had 2 or more lines of IOD at baseline, 17 (74%) were treated with spectacles alone, and six (26%) were treated with patching, atropine, or both in addition to spectacles. Twenty of these children had IOD measured at one year, and 2 or more lines of IOD persisted after one year in five (36%) of the 14 treated with spectacles alone and in two (33%) of the six who also had patching, atropine, or both.

Of the 90 children who had less than 2 lines of IOD at baseline, 83 (92%) were treated with spectacles alone and seven (8%) were treated with patching and spectacles. Eighty-one of these children had IOD measured at one year, and 2 or more lines of IOD were present after one year in 10 (13%) of the 75 treated with spectacles alone and in one (17%) of the six who also had patching.

• **STEREOACUITY:** Of the 94 children who had stereoacuity tested at both baseline and the one-year examina-

TABLE 3. (*Continued*)

Characteristics	Binocular Acuity					
	No. of Lines of Improvement at One Year*			20/25 or Better at Any Follow-up Visit†		
	n	Mean	*P* value	n	n (%)	*P* value
Stereoacuity, seconds of arc‖			.52			.47
40	4	3.7		4	3 (75)	
60	5	3.6		5	4 (80)	
100	4	3.5		5	5 (100)	
200	5	2.9		5	5 (100)	
400	9	3.2		10	6 (60)	
800	13	4.0		15	11 (79)	
None detected (>800)	57	4.1		66	43 (71)	

D = diopters.

*N is the number of children completing the study in the specified strata. *P* values from individual linear regression models with lines of binocular acuity improvement as the dependent variable and baseline binocular visual acuity and the factor of interest as covariates. Age, hypermetropia, astigmatism, and anisometropia were evaluated as continuous data. Stereoacuity was evaluated dichotomously as >800 seconds of arc vs 800 seconds of arc or better.

†N is the number of children in the study in the specified strata (i.e., includes all children regardless of whether they completed the study). Percentages cited are cumulative probabilities derived from Kaplan-Meier product-limit method. *P* values from individual proportional hazards regression models the proportion of children achieving binocular acuity 20/25 or better as the dependent variable and baseline binocular visual acuity and the factor of interest as covariates. Age, hypermetropia, astigmatism, and anisometropia were evaluated as continuous data. Stereoacuity was evaluated dichotomously as >800 seconds of arc vs 800 seconds of arc or better.

‡Analysis of hypermetropia was limited to children who were eligible for the study based on significant hypermetropia (spherical equivalent, ≥4.00 D) in both eyes. Hypermetropia refers to the average amount of spherical equivalent between the two eyes.

§Analysis of astigmatism was limited to children who were eligible for the study based on significant astigmatism (≥2.00 D) in both eyes. Astigmatism refers to the average amount of astigmatism between the two eyes.

‖Three children were unable to perform stereoacuity testing.

tion, stereoacuity had improved a mean of 1.9 levels (95% CI, 1.4 to 2.3), with 56 children (60%) improving two levels or more (Table 4). Improvement in stereoacuity was associated with improvement in binocular visual acuity ($P = .02$).

TABLE 4. Stereoacuity Outcomes during One Year of Spectacle Wear in Patients 3 to Less than 10 Years of Age with Previously Untreated Bilateral Refractive Amblyopia (n = 113)

Change in Stereoacuity from Baseline to One Year, levels*	
Mean (SD)	1.9 (2.1)
Range	−4.0 to 6.0
Stereoacuity at one year (seconds of arc), n (%)†	
40	13 (13)
60	12 (12)
100	18 (19)
200	11 (11)
400	17 (18)
800	3 (3)
>800	23 (24)

SD = standard deviation.

*Negative values represent a decrease in stereoacuity. A change in stereoacuity could not be calculated for 19 patients: five were unable to perform testing (three at baseline and two at one year) and 14 did not have testing completed at one year.

†Sixteen children were missing stereoacuity outcomes at one year: two children were unable to perform testing and 14 did not have testing completed.

DISCUSSION

IN THIS PROSPECTIVE, MULTICENTER STUDY OF 113 CHILDREN with previously untreated bilateral refractive amblyopia, binocular visual acuity improved an average of 3.9 lines after one year of treatment, with spectacles as the sole treatment in all but 13 children. Binocular visual acuity of 20/25 or better was achieved by 73% of children within one year of starting treatment. Although there was no untreated control group, the observed improvement substantially exceeded any expected learning or age effect.[10–12] Visual acuity improvement was accompanied by a corresponding improvement in stereopsis, with 60% of children improving by at least two levels on the Randot Preschool Stereoacuity Test. Smaller series of patients with similar inclusion criteria have also demonstrated improvement in bilateral refractive amblyopia. Klimek and associates found that 21 (58%) of 36 children with bilateral refractive amblyopia achieved a visual acuity of 20/25 or better in at least one eye with a mean follow-up of

3.3 years.[8] Schoenleber and associates reported that 10 (83%) of 12 children improved to 20/40 or better in both eyes with a mean follow-up of 22 months.[5] Our study had 12 months of follow-up and was not designed to assess maximal improvement on treatment. Therefore, additional improvement in visual acuity, stereopsis, or both may occur beyond one year.

At baseline, the children in our cohort had modestly reduced visual acuity (mean, 20/63), and the acuity deficit usually was symmetrical (79% had less than 2 lines of IOD). There was an approximately equal number of children with high bilateral hypermetropia only and those with high bilateral astigmatism only. The refractive error characteristics of our cohort differs from that of other samples that included a larger proportion of children with high astigmatism such as Native Americans.[13]

Binocular visual acuity was our primary outcome because we believe it best represents visual function in a real-world setting. Most children had symmetrical amblyopia at baseline, so it is not surprising that there was little difference between monocular and binocular visual acuity outcomes. Improvement of bilateral amblyopia with spectacles alone can result in resolution of amblyopia in one eye and persistent amblyopia in the other eye, requiring additional amblyopia treatment with occlusion therapy or atropine. However, only 13 (12%) of 113 children in our cohort received patching, atropine treatment, or both, in contrast to 13 (36%) of 36 children in the study by Klimek and associates.[8] This difference may be because our protocol specifically discouraged investigators from treating with patching or atropine until the visual acuity in each eye stopped improving.

The mechanism of bilateral refractive amblyopia is presumed to be pattern vision deprivation; that is, failure of both eyes to achieve a clear foveal image results in abnormal development of the visual cortex.[2] Children with uncorrected hypermetropia without significant astigmatism generally can accommodate sufficiently to achieve clear retinal images and thus avoid the development of amblyopia. It is not known why some children with uncorrected hypermetropia develop amblyopia and some do not. Perhaps reduced accommodative amplitudes, which have been found in some children with bilateral refractive amblyopia, play a role.[5,6] The relatively large amount of accommodation required for clear vision can result in the development of refractive accommodative esotropia in some children with high hypermetropia. It also has been suggested that children with bilateral hypermetropic amblyopia unconsciously choose orthophoria and bilaterally reduced vision over esotropia with diplopia.[5] The presence of strabismus generally prompts referral to an eye doctor, whereas those children with high hypermetropia without strabismus can be detected by screening programs.[14] When strabismus is absent, noncompliance with glasses can be a problem and parents may not acknowledge the need for treatment because there is no obvious disability.

In cases of bilateral amblyopia with concomitant strabismus, abnormal binocular interaction with suppression also may contribute to the development of amblyopia in the nonpreferred eye. We observed strabismus in 15 (13%) of 113 children in our study, 12 of whom had esotropia. In contrast, Klimek and associates detected strabismus in 23 (64%) of 36 children, 22 of whom had esotropia.[8] However, their study included only children with hypermetropia of 4.50 D or more, whereas we included children with astigmatism without significant hypermetropia.

In conclusion, we observed substantial improvement of binocular best-corrected visual acuity during treatment of bilateral refractive amblyopia with spectacle correction; 73% of children three to less than 10 years of age achieved visual acuity of 20/25 or better after one year. Improvements in visual acuity and stereopsis generally were achieved with spectacles alone; only 12% of the children in our cohort received additional amblyopia treatment with patching or atropine.

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