



Published in final edited form as:

J AAPOS. 2010 December ; 14(6): 494–497. doi:10.1016/j.jaapos.2010.10.004.

The clinical profile of amblyopia in children under 3 years of age

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Abstract

Purpose—Amblyopia in children ≥ 3 years has been well described, but less is known about amblyopia in children < 3 years old. Here we describe the clinical characteristics of a large cohort of children with amblyopia < 3 years of age and compare them with a previously described PEDIG amblyopic cohort aged 3 to 6 years.

Methods—250 consecutive children with amblyopia < 3 years were referred by 16 pediatric ophthalmologists.

Results—The mean age at the initial diagnosis of amblyopia was 1.2 ± 0.7 years. The cause of amblyopia was strabismus in 82%, anisometropia in 5%, and combined mechanism in 13%. Compared to the 3- to 6-year-old cohort, the proportion of amblyopia attributable to strabismus was significantly higher ($p < 0.001$), while both anisometropia and combined mechanism amblyopia were significantly less common ($p < 0.001$). Overall, 61% of amblyopia was diagnosed at the same visit in which strabismus and/or anisometropia was initially diagnosed; an additional 21% of amblyopia was diagnosed at the first follow-up visit 1–3 months later. Compared to the 3- to 6-year-old cohort, amblyopic eye refractive error was significantly lower.

Conclusions—Strabismic amblyopia was diagnosed much more commonly than anisometric and combined-mechanism amblyopia in children < 3 years. Anisometric amblyopia may be difficult to detect in children < 3 years, and/or strabismic amblyopia may be over-diagnosed by fixation preference. Alternatively, anisometropia may develop more commonly after 3 years of age or may require greater duration to cause amblyopia.

Amblyopia is a loss of vision in one or both eyes caused by conditions that affect the normal development of vision, including strabismus, anisometropia, a combination of strabismus and amblyopia or, less commonly, visual deprivation. In 2002 the Pediatric Eye Disease Investigator Network (PEDIG) described characteristics of amblyopic children ages 3–6 years by summarizing the baseline data from amblyopic children with strabismus, anisometropia, or both enrolled in a treatment study at 47 US centers.¹ However, there are few published data on the characteristics of amblyopic children under 3 years of age. The primary aim of this study was to describe the demographic and clinical characteristics of a

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Presented at the 36th Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus, Orlando, Florida, April 14-18 2010.

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cohort of amblyopic children under 3 years of age with strabismus, anisometropia or both. A secondary aim was to compare these characteristics with those from the previously described PEDIG cohort of 3- to 6-year-old amblyopic children.¹

Subjects and Methods

Participants were a subset of 463 children under 3 years of age who were enrolled consecutively in a study of strabismus and anisometropia as amblyogenic factors at the Retina Foundation of the Southwest. Children were referred to the study with strabismus, anisometropia, or both by 16 pediatric ophthalmologists in northern Texas. The subset for the present study was composed of the 250 children in this cohort who were diagnosed with amblyopia before age 3 years by the referring ophthalmologist. Clinical characteristics were recorded at the visit at which amblyopia was first diagnosed by the referring pediatric ophthalmologist; none had a prior diagnosis of amblyopia or prior treatment for amblyopia. All participants were otherwise healthy and had no developmental delay. Children with bilateral amblyopia due to high refractive error were excluded. Table 1 summarizes information about the composition of this <3-year-old cohort and provides a comparison with the 3- to 6-year-old cohort described by PEDIG.¹ Both this study and the PEDIG study included children with strabismic, anisometropic, or combined-mechanism amblyopia referred by multiple community- and university-based pediatric ophthalmologists. Two minor differences between the studies were the inclusion of children who had <2 months amblyopia treatment in the PEDIG study versus no prior amblyopia treatment in the present study and the exclusion of myopic children from the PEDIG cohort versus no exclusion based on refractive error in this study.

In the cohort less of than 3 years of age, amblyopia was diagnosed based on fixation preference; that is, poor or fair fixation by one eye or failure to maintain fixation for >2 seconds when the fellow eye was uncovered. Fixation preference of children with orthotropia or small angle (<10^Δ) strabismus, and children with intermittent strabismus who fused during the examination, was evaluated with a 10^Δ–12^Δ base-down loose prism. While fixation preference may be an imperfect method for the diagnosis of amblyopia,^{2,3} it is currently the most widely accepted method for deciding which children age <3 years with strabismus and/or anisometropia need amblyopia treatment.⁴

This research protocol observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of UT Southwestern Medical Center. The Retina Foundation of the Southwest is a HIPAA-exempt institution.

Statistical Methods

Continuous data from each study were compared using analysis of variance methods. Pairwise comparisons among types of amblyopia were performed by *t*-tests, with Bonferroni corrections for multiple comparisons. Categorical data were compared using χ^2 or Fisher exact tests. Pairwise comparisons of categorical data (proportions) were performed by *z*-tests, with Bonferroni corrections for multiple comparisons.

Results

Demographic Characteristics

The amblyopic <3-year-old cohort included approximately equal numbers of male and female participants, 49.6% versus 50.4, similar to the PEDIG 3- to 6-year old cohort¹ (Table 2). Both studies also had cohorts with similar race and ethnicity; 81% white in this study and 83% white in the PEDIG study. Gestational age at birth was consistent with full-term birth in the children <3 years of age, but not reported in the PEDIG study. Unlike the PEDIG 3- to

6-year-old group, diagnosis of amblyopia in right and left eyes was approximately equally prevalent in the <3 year age range.

Amblyogenic Factor

In the <3-year-old cohort, 82% of amblyopia was associated with strabismus, 5% with anisometropia, and 13% with combined mechanisms (Table 2). This is strikingly different from the PEDIG 3- to 6-year-old cohort, where only 38% of amblyopia was associated with strabismus, 37% with anisometropia, and 24% with combined mechanism ($p < 0.001$ for each of the three paired comparisons). Among children with strabismus in the <3-year-old cohort, 62% had infantile esotropia (onset ≤ 6 months of age), 22% had accommodative esotropia, 10% had acquired nonaccommodative esotropia (onset ≥ 7 months of age), and 6% had other types of strabismus.

Diagnosis of strabismus in the <3-year-old cohort was made at a mean age of 0.7 year; 66% were diagnosed by 1 year, an additional 29% by 2 years, and the remaining 5% by 3 years (Table 3). The mean deviation by simultaneous prism and cover test in the strabismic amblyopia group was $41^{\Delta} \pm 6^{\Delta}$ at near and $38^{\Delta} \pm 18^{\Delta}$ at distance.

Anisometropia was diagnosed later (1.1 years) with only 50% identified by 1 year, 42% by 2 years, and 8% by 3 years. Similarly, only about half (53%) of the cases of strabismus in combination with anisometropia were identified during the first year of life, 32% during the second year, and 16% during the third year. The mean deviation by simultaneous prism and cover test in the combined mechanism amblyopia group was $35^{\Delta} \pm 17^{\Delta}$ at near and $29^{\Delta} \pm 11^{\Delta}$ at distance. The combined mechanism group had significantly smaller angles of deviation than the strabismic amblyopia group, at distance fixation, but not at near.

Amblyopia

In the <3-year-old cohort, 61% of amblyopia was diagnosed on the initial visit; i.e., on the same visit at which the amblyogenic factor was first diagnosed by the pediatric ophthalmologist. An additional 21% of amblyopia was diagnosed on the first follow-up visit, 4–12 weeks later. Only 17% of amblyopia was first diagnosed 4–24 months after the initial visit, including the 36 children who were first diagnosed with amblyopia following strabismus surgery. Overall, 19% were diagnosed with amblyopia on the basis of poor or fair fixation in the amblyopic eye and 81% on the basis of failure to maintain fixation with the amblyopic eye (86% of the strabismic children and 44% of the anisometropic and combined mechanism children).

Refractive Error

In the <3-year-old cohort, 8% of amblyopic eyes were myopic, 47% had low hyperopia ($< +3.00$ D), 25% were moderately hyperopic ($+3.00$ to $+4.88$ D), and 20% had high hyperopia ($\geq +5.00$ D). There were no significant differences in refractive error of the amblyopic eye (spherical equivalent) among the <3-year-old children with different amblyogenic factors. Amblyopic eyes of <3-year-old children had significantly less hyperopia than 3- to 6-year-old amblyopic children in the PEDIG study.¹ Among fellow eyes, 7% were myopic, 53% had low hyperopia ($< +3.00$ D), 24% were moderately hyperopic, and 16% had high hyperopia. Children <3 years of age with strabismic and combined mechanism amblyopia had significantly more fellow eye hyperopia than children with anisometropic amblyopia. Overall, fellow eyes of <3-year-old children had significantly less hyperopia than 3- to 6-year-old amblyopic children in the PEDIG study.¹ Anisometropia of 1.00–2.99 D was present in 12% of amblyopic children <3 years of age; ≥ 3.00 D anisometropia was present in 6%. Overall, the magnitude of anisometropia in children with anisometropic amblyopia was significantly greater in the <3 year cohort than in the PEDIG 3- to 6-year-old cohort¹;

there was no significant difference in magnitude of anisometropia for combined mechanism amblyopia.

By eligibility criterion, none of the <3-year-olds had prior amblyopia treatment. The initial treatment prescribed by the referring physicians included alternate occlusion (21%), occlusion of the fellow eye (48%, including 26% for 1–2 hours per day, 19% for 3–5 hours per day, and 3% 6–8 hours per day), atropine (5%), and glasses (31%).

Discussion

Strabismic amblyopia was diagnosed much more commonly than anisometric or combined-mechanism amblyopia in children <3 years of age. This finding is in sharp contrast to the PEDIG description of amblyopia in 3- to 6-year-old children, which reported approximately equal proportions of patients with amblyopia due to strabismus and anisometropia, with about a quarter of the patients having elements of both.¹ Two UK studies of amblyopic children, which included younger children than the PEDIG study, found the cause to be strabismus in a higher percentage than the PEDIG study (45%–57%), a lower percentage to be anisometric (17%), and about the same percentage to be combined mechanism (27%–35%).^{5,6} Looking at all four studies together suggests that one source of the differences in the proportion of amblyopia attributable to strabismus may be age; that is, 82% in the present study where the mean age at diagnosis of amblyopia was 0.8 year, 45% to 57% in the UK studies,^{5,6} with a mean age at diagnosis of 3.3 years and 3.6 years, and 38% in the PEDIG study¹ with a mean age at diagnosis of 5.3 years.

The low percentage of amblyopia attributable to anisometropia in the <3 year age group appeared not to be a result of marked under-referral of anisometropia in this age range, because a much larger number of children with anisometropia (without amblyopia) were referred during the same period. Recall that the 250 children described in the present study were a subset drawn from 463 children under 3 years of age who were enrolled consecutively in a study of strabismus and anisometropia as amblyogenic factors. Within the larger cohort of 463 children, the 67 children with anisometropia were referred, but only 18% were diagnosed with amblyopia. In contrast, almost half of the 396 children with strabismus or strabismus with anisometropia had a significant fixation preference and were diagnosed with amblyopia. Nevertheless, it is also possible that, in some children, anisometropia itself may develop later, and become an etiologic factor for amblyopia after 3 years of age. One additional possible explanation for the finding of a lower proportion of anisometric amblyopia in younger children is that anisometropia may require longer duration than strabismus to cause amblyopia. Alternatively, there is some recent evidence that fixation preference may under-diagnose anisometric amblyopia and/or overdiagnose strabismic amblyopia.^{2,3} Our ongoing longitudinal study of children with amblyogenic factors will allow us to examine these alternative hypotheses.

Two other characteristics differed between the <3-year-old amblyopic cohort in the present study and the previously reported 3- to 6-year-old PEDIG amblyopic cohort. First, the younger children had less hyperopia in both their amblyopic and fellow eyes than the older children. This finding may have resulted from a lower prevalence of accommodative esotropia in the <3-year-old amblyopic cohort than in the 3- to 6-year-old PEDIG amblyopic cohort. Second, the younger children with anisometric amblyopia had significantly more anisometropia than the older children. This may have been a consequence of PEDIG's exclusion of myopic children, which necessarily curtailed the range of anisometropia observed in their cohort.

The diagnosis of amblyopia was based on fixation preference, specifically poor or fair fixation by one eye or failure to maintain fixation for >2 seconds when the fellow eye was uncovered. While the accuracy of fixation preference as a diagnostic method for amblyopia has been questioned recently,^{2,3} those studies were performed in a screening environment of mostly normal children, and the few children identified as amblyopic were primarily children with anisometropic amblyopia. In contrast, our clinical environment had a high prevalence of strabismic amblyopia. A more recent study⁷ reported better sensitivity of fixation preference in strabismic children (73% for deviations $\geq 10^\Delta$ and 90% for deviations $< 10^\Delta$, with corresponding specificities of 78% and 65%). Moreover, fixation preference is still currently accepted as the mainstay of clinical diagnosis of amblyopia for children <3 years of age.⁴

The clinical profile of amblyopic children <3 years of age presented here is based on a cohort with broad eligibility criteria, with the intention to include all amblyopic children <3 years of age with strabismus, anisometropia, or both who were otherwise healthy and developmentally normal. Children were referred to the study by 16 pediatric ophthalmologists, located in University, hospital clinic, and private practice settings that serve the diverse population in North Texas. Only children who had not been previously diagnosed or treated for amblyopia were enrolled. With a few minor exceptions, these criteria were similar to those used in an earlier PEDIG study that described the clinical profile of 3- to 6-year old amblyopic children.¹ Our data on the clinical profile of amblyopia in children younger than 3 years may be useful for the planning of future clinical trials of amblyopia treatment in this age range.

Acknowledgments

Supported by grants from the National Eye Institute (EY05236 EB and EY018810 JMH) and from Research to Prevent Blindness, New York, NY (JMH as an Olga Keith Weiss Scholar and an unrestricted grant to the Department of Ophthalmology, Mayo Clinic).

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Table 1

Enrollment of Amblyopic Children in This Study Compared with Children Enrolled in the PEDIG (2002) Study

This Study	PEDIG (2002)
Strabismus, anisometropia, or combined	Strabismus, anisometropia, or combined
Referred by 16 sites	Referred by 47 sites
Enrolled in amblyopia study	Enrolled in amblyopia study
Community- and university-based	Community- and university-based
250 children	419 children
Age <3 years	Age 3–6 years
No prior treatment	≤2 months prior amblyopia treatment
Any refractive error (6% myopic)	Myopia excluded

Demographic and clinical characteristics of amblyopic children <3 years of age, and characteristics previously reported for 3- to 6-year olds

Table 2

	Ambyopic <3 years of age		PEDIG (2002) 3- to 6-year-olds ¹		
Male/Female (%)	49.6/50.4		53.9/46.1		<0.004
Race/Ethnicity (%)					
Non-Hispanic white	81		83		
African American	3		6		
Hispanic	12		6		<0.01
Asian	2		2		
Mixed/other	2		3		
Gestational age at birth (weeks, mean ± SD)					
	39.0±1.6		---		---
Affected eye, RE/LE (%)					
	48.8/50.2		41.1/58.9		<0.004
Amblyogenic factor, strabismus/anisometropia combined (%)					
	82.5/13		38.37/24		<0.0001

Note: Demographic characteristics of the <3-year-old amblyopic children in this study and 3- to 6-year-old children in the PEDIG study¹ were compared using Fisher exact (sex, affected eye) or χ^2 tests (race/ethnicity, amblyogenic factor).

¹The clinical profile of moderate amblyopia in children younger than 7 years. Arch Ophthalmol 2002;120:281-7.

Table 3

Clinical characteristics by cause of amblyopia for amblyopic children <3 years of age, and characteristics previously reported for 3- to 6-year-olds¹

	Amblyopic children <3 years				PEDIG 3- to 6-year-olds ¹				Pairwise comparisons ^{**}					
	S	A	C		S vs A	S vs C	A vs C		S	A	C	S vs S	A vs A	C vs C
Age at diagnosis of amblyogenic factor (years, mean ± SD)	0.7 ± 0.6	1.1 ± 0.6	1.2 ± 0.7		0.02	0.0003	0.93		---	---	---	---	---	---
Near deviation (PD ± SD)	40.7 ± 5.9	ortho	34.8 ± 16.9		---	0.05	---		---	---	---	---	---	---
Distance deviation (PD ± SD)	38.1 ± 17.6	ortho	29.2 ± 11.1		---	0.02	---		---	---	---	---	---	---
Age at diagnosis of amblyopia (years, mean ± SD)	0.9 ± 0.6	1.3 ± 0.7	1.2 ± 0.7		0.04	0.03	0.67		5.1 ± 1.2	5.4 ± 1.0	5.2 ± 1.0	---	---	---
Months before diagnosis of amblyopia (mean ± SD)	2.1 ± 3.9	2.6 ± 3.4	0.4 ± 1.0		0.67	0.014	0.002		---	---	---	---	---	---
Fixation Preference (%)														
Poor or Fair fixation	18	50	40						---	---	---	---	---	---
Not maintained	82	50	60		0.02	0.008	0.74		---	---	---	---	---	---
Amblyopic eye spherical equivalent (D ± SD)	2.62 ± 2.08	0.95 ± 6.27	3.43 ± 4.42		0.02	0.09	0.15		4.38 ± 2.17	4.78 ± 1.94	4.21 ± 2.33	< 0.0001	< 0.0001	< 0.0001
Fellow eye spherical equivalent (D ± SD)	2.59 ± 2.05	0.94 ± 2.11	3.05 ± 1.76		0.007	0.23	0.002		2.88 ± 2.08	2.80 ± 2.08	2.58 ± 2.03	< 0.0001	0.05	1.00
Anisometropia spherical equivalent (D ± SD)	0.16 ± 0.24	4.89 ± 2.61	2.24 ± 2.28		< 0.0001	< 0.0001	0.004		1.53 ± 1.48	2.01 ± 1.74	1.68 ± 1.61	< 0.0001	< 0.0001	0.79

S, strabismic; A, anisometropic; C, combined; PD, prism diopters; ortho, orthotropic; D, diopters.

* Pairwise comparisons among strabismic (S), anisometropic (A), and combined mechanism (C) amblyopia groups in the present study. Pairwise comparisons with $p < 0.017$ are statistically significant using the Bonferroni correction for multiple pairwise comparisons (shown in bold).

** Pairwise comparisons between <3-year-old amblyopic children in this study and 3- to 6-year-old children from the PEDIG study¹ for strabismic (S), anisometropic (A), and combined mechanism (C) amblyopia groups. Pairwise comparisons with $p < 0.017$ are statistically significant using the Bonferroni correction for multiple pairwise comparisons (shown in bold).