Risk Factors for Accommodative Esotropia among Hypermetropic Children

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Purpose. Identification of risk factors for accommodative esotropia may help to determine which children with hyperopia may benefit from early spectacle correction or preventive therapy.

Methods. Participants in the *family history study* were 95 consecutive patients, aged 18 to 60 months, with accommodative esotropia. Participants in the *binocular sensory function study* were a subgroup of 41 children enrolled in the family history study within 1 month of onset, while the esodeviation was still intermittent. Participants in the *hypermetropia study* were 345 consecutive patients, ages 12 months to 8 years, with refractive error of +2.00 D or greater and no esodeviation before age 12 months.

Results. In the *family history study*, 23% of children with accommodative esotropia had an affected first-degree relative, and 91% had at least one affected relative. In the *binocular sensory function study*, random-dot stereoacuity was abnormal in 41% of children, whereas an abnormal motion VEP, Worth 4-dot, or positive 4-PD base-out prism responses were present in 4% or less of the children. In the *hypermetropia study*, patients with a mean spherical equivalent of < +3.00 D and significant anisometropia had a 7.8-fold increased risk for accommodative esotropia over nonanisometropic patients.

Conclusions. A positive family history, subnormal random-dot stereopsis, and hypermetropic anisometropia each pose a significant risk for the development of accommodative esotropia. Assessment of these risk factors in conjunction with refractive screening should help to identify those children who are most likely to benefit from early spectacle correction or preventive treatment. (*Invest Ophthalmol Vis Sci.* 2005;46:526–529) DOI: 10.1167/iovs.04-0618

Treatment with spectacle correction of ≥+4.00 D of hypermetropia has been shown to reduce the prevalence of accommodative esotropia in children aged 4 years by >50% and potentially reduces the risk of hypermetropic ametropic amblyopia.[1] Despite the potential benefit of early intervention, this treatment approach has not been widely adopted for at least two reasons. First, the prevalence of accommodative esotropia among children who had hypermetropia of ≥+4.00 D during infancy is low (10%–20%),[1,2] and so the placement of spectacles on all children with ≥+4.00 D hypermetropia would result in the treatment of many children who are not at risk for development of accommodative esotropia. Unnecessary treatment with spectacle correction during infancy and early childhood is expensive, places a compliance burden on families, and may interfere with emmetropization, especially if refractive error is fully corrected.[3] Atkinson et al.[4] found a significantly slower course of emmetropization among hyperopic infants who were undercorrected by 1 D, although this was a transient effect. By 36 months of age, emmetropization was similar in the two groups. Full correction of refractive error may have a larger impact on emmetropization, since the greater reduction in accommodative demand may minimize the visual feedback from optical defocus that is thought to play a role in compensatory eye growth.[5–7]

Second, many children who have accommodative esotropia have hypermetropic refractive errors less than +4.00 D and would not be treated with this approach. For example, more than half of the patients in a group of 68 children with accommodative esotropia reported by Raab[8] had less than +4.00 hypermetropia on the initial visit.

Identification of additional risk factors for accommodative esotropia could play an important role in determining which children with hypermetropia <+4.00 D may benefit from early preventive treatment with spectacles. The purpose of this study was to examine three potential risk factors, commonly associated with accommodative esotropia[9–11] that might be used along with refractive screening to identify children at highest risk for accommodative esotropia. The risk factors examined were family history, abnormal binocular sensory function, and significant (>1.00 D) anisometropia.

Methods

Subjects

Participants in the *family history study* were 95 consecutive patients with accommodative esotropia, ages 18 to 60 months, enrolled in a prospective study of accommodative esotropia. Participants in the *binocular sensory function study* were a subgroup of those enrolled in the *family history study* who had a visit within 1 month of detection of the esotropia by the parent or pediatrician and within 1 month of diagnosis of accommodative esotropia by a pediatric ophthalmologist, while the esodeviation was still intermittent (n = 41). The rationale for selecting this subgroup for study was that any binocular sensory abnormalities present at this early stage (when the child still enjoyed orthophoria throughout most of the waking hours) may have been present before the onset of the intermittent deviation and therefore represented a true risk factor.

All participants in the studies of family history and binocular sensory function had onset of accommodative esotropia at 18 to 48 months of age associated with hypermetropia and/or high accommodative convergence/accommodation (AC/A) ratio. They were diagnosed by a pediatric ophthalmologist and referred to the Retina Foundation of the Southwest for participation in research studies of sensory outcomes after treatment during the years 1988 to 1998. None of the patients had known neurologic defects or other coexisting disease.

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Participants in the *hypermetropia study* were drawn from a separate cohort composed of 345 consecutive new patients >1 year of age presenting to the Ophthalmology Service of Children's' Medical Center, Dallas Texas for the 42-month period from January 1, 1995, to June 30, 1998.[12–14] Patients were eligible if they had an overall refractive error of +2.00 D or greater (mean spherical error calculated as spherical error + 0.5 × astigmatic error; average of both eyes), and no history of or documented esodeviation before age 12 months; 345 patients were included in this study. Patients enrolled ranged in age from 12 months to 8 years.

Informed consent was obtained from one or both parents before the child's participation. The research protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

Family History

Parents of children with accommodative esotropia were asked to fill out a brief questionnaire about the family history of strabismus and other ocular disorders among close-degree relatives of the affected child (siblings, parents, grandparents, aunts, uncles, and cousins). These data were used to construct a preliminary pedigree. A staff member reviewed the pedigree with the parent(s), and corrections were made as needed. Accompanying siblings were examined.

On follow-up visits to the laboratory and/or by telephone, directed interviews were conducted with the parents or other relatives to provide further additions and clarifications to the pedigrees. Experienced staff conducted all interviews. Directed interviews included detailed questions on the nature of the strabismic deviation, the age of onset of strabismus, any surgical or nonsurgical treatment, refractive error, age at which glasses were initially prescribed, and whether there were any other familial medical conditions.

Only family members who were reported to have eyes that were misaligned toward the nose, who had had onset during the preschool age range (18 months to 48 months), and who had been treated with glasses that magnified the eyes were classified as affected by accommodative esotropia. Family members with other forms of strabismus or amblyopia or for whom insufficient detail was available regarding the character of the strabismic deviation, the age at onset of strabismus, or the type of treatment they received were not classified as affected. Although ophthalmic examinations of all family members may have provided other useful information, in some cases neither hypermetropia ≥ +4.00 D nor esotropia persisted into adulthood after a successful early-childhood course of treatment. Pedigree analysis was performed to determine the prevalence of affected relatives as a function of degree of relationship with the proband.

Binocular Sensory Function

All children wore spectacle correction that fully corrected their intermittent esodeviations during binocular sensory testing. Random-dot stereoacuity was evaluated, using the Randot test (version 2) and the Preschool Randot Stereoacuity Test (for children aged ≥3 years) or the Randot Stereocards[15] (for children <3 years of age) (all from Stereo Optical, Inc., Chicago, IL). Fusion was assessed with the Worth 4-dot test at near (33 cm) and, when possible, based on the child's age, at distance (3 m) and by the 4-PD base-out test. Monofixation (absence of foveal fusion) was determined by examining the asymmetry of the motion VEP in response to a 1-cyc/deg sine wave grating undergoing quadrature motion at 6 Hz. Asymmetry in the motion VEP response has been shown to be strongly associated with suppression of the W4D at distance but not at near fixation, deficient or absent stereopsis, and a positive 4-PD base-out test (i.e., with the clinical hallmarks of monofixation syndrome).[16,17] Data were summarized by calculating the proportion of children with abnormal results on each test.

Hypermetropia Study

Each patient was evaluated, using cycloplegic refraction, to determine overall spherical equivalent refraction and overall spherical equivalent of anisometropia. In addition, an ocular motility examination was performed to determine the presence or absence and constancy of esotropia, and acuity or fixation preference testing was completed to determine presence or absence of amblyopia. Significant anisometropia was defined as being 1.00 D or more. This amount of anisometropia was chosen as "significant," because it has been reported to increase the prevalence of amblyopia and reduces binocularity in patients without strabismus.[12] The effects of moderate (≥1 to <2 D) and large (≥2 D) anisometropia were also compared with each other and with patients without anisometropia. The relative risk (derived from the odds ratio) of developing esotropia was determined.[18]

Logistic regression analysis was used to estimate the odds ratio for the adverse outcome of esotropia between subjects with and without anisometropia using a statistical analysis program (SAS Institute, Cary, NC). Age, mean spherical equivalent, and amblyopia were found to be associated with esotropia and considered to be possible confounders in the analysis. Adjusted odds ratios for esotropia were computed in a logistic regression model, with esotropia (yes/no) as the dependent variable; anisometropia (yes/no), age, and mean spherical equivalent as continuous variables; and presence of amblyopia (yes/no) as the independent variable. Because esotropia was not a rare outcome, the adjusted odds ratios were corrected to relative risks.

Table 1. Family History by Directed Interview

	%
Prevalence of accommodative ET among first-degree relatives	22
Prevalence of accommodative ET among second-degree relatives	10
Proband has first-degree and/or second-degree affected relative	77
Proband has an affected relative	91

ET, esotropia.

Results

Family History

Of the 95 families invited to participate, 9 were excluded from the analyses. Two parents refused to provide sufficient information, two of the probands were adopted, three probands had one adopted parent, and two probands had a family history of other heritable conditions that might be associated with strabismus (one craniofacial disorder and one neurologic disorder). In the remaining 86 families studied, all interviews were completed to the level of the first- and second-degree relatives (including parents, siblings, grandparents, aunts, and uncles), and 44 of the pedigrees were completed to the level of the third- to fifth-degree relatives (including great grandparents, cousins, and more distant blood relatives).

Data from a total of 2828 blood relatives were obtained, with a mean of 54 blood relatives per family. The total number of affected individuals was 214 (106 male, 108 female). Results are summarized in Table 1. Overall, 19 of 86 probands (22%) had affected first-degree relatives and 66 of 86 probands (77%) had affected first- and/or second-degree relatives. In the 44 pedigrees completed to the level of third- to fifth-degree relatives, 40 (91%) of 44 probands had at least one affected relative.

Binocular Sensory Function

The mean (±SD) age of the 41 children tested at the onset of intermittent accommodative esotropia was 2.4 ± 0.6 years, and the range was 1.5 to 3.6 years. The percentage of children with normal and abnormal outcomes on each of the four tests is summarized in Table 2. Not all children were cooperative for all four tests. The number of children who successfully completed each test is provided. At the onset of intermittent eso-

TABLE 2. Binocular Sensory Function at the Onset of Intermittent Accommodative Esotropia

Test	*n*	% Abnormal Results
Random-dot stereoacuity	39	41.0
Worth 4-dot	35	0.0
4 PD base-out prism	28	3.6
Motion VEP symmetry	37	0.0

deviation, random-dot stereoacuity was abnormal in 41% of children. No abnormal results were found for motion VEP response symmetry or fusion assessed by the Worth 4-dot test. Only 4% of children showed an abnormal 4-PD base-out prism test response.

Hypermetropia

Anisometropia (≥1.00 D) was present in 28% (97/345) of patients, whereas esotropia was present in 61% of patients (210/345). The relative risk (RR) for development of accommodative esotropia (either intermittent or constant) when anisometropia was present compared with when it was absent is summarized in Table 3. Anisometropia (≥1.00 D) increased the RR for development of accommodative esotropia to 1.68 when adjusted for age, overall spherical equivalent, and amblyopia. This increased RR was the same for patients with 1.00 to <2.00 D of anisometropia as for patients with ≥2.00 D of anisometropia.

When the data were stratified by mean hypermetropic spherical equivalent (Table 4), anisometropia was found to significantly increase the RR of development of accommodative esotropia at lower amounts of hypermetropia. Patients with a mean SE of <+3.00 D and anisometropia had a 7.8 times increased RR for accommodative esotropia compared with nonanisometropic patients with the same overall SE. This was significantly higher than the effect of anisometropia on the RR for development of accommodative esotropia in more hypermetropic individuals (RR = 1.49 for >+3.00 D spherical equivalent; $P = 0.017$). When the data were further stratified into 1-D groups, the largest effect on RR for development of accommodative esotropia was again most notable in patients with lower hypermetropic refractive error (Table 4).

Anisometropic patients were more likely to be amblyopic than nonanisometropic patients (82%, 79/97 vs. 35%, 87/248). In addition esotropic patients were also much more likely to be amblyopic than nonesotropic patients (73%, 153/210 vs. 10%, 13/135). However, because of the significant association between amblyopia and anisometropia (82% of anisometropic patients were amblyopic) and the strong correlation between both of these variables and esotropia (82% of anisometropic patients and 93% of amblyopic patients were esotropic), there was little opportunity to examine the effect of anisometropia free of amblyopia. Nevertheless, in the 179 nonamblyopic patients, anisometropia increased the RR for esotropia to 2.14, consistent with anisometropia as an independent risk factor.

DISCUSSION

Family history, subnormal random-dot stereopsis, and, in children with hypermetropia < +4.00 D, anisometropia, each resulted in a significant increase in the risk for the development of accommodative esotropia. More than 75% of children with accommodative esotropia had an affected parent, sibling, grandparent, aunt, or uncle, and >90% of children with accommodative esotropia had at least one affected relative. The 22.9% prevalence of first-degree affected relatives reported herein is similar to the 18% reported by Aurell and Norrsell.[19]

Although the data support family history as a significant risk for the development of accommodative esotropia, this does not imply that all children with a positive family history necessarily are candidates for intervention. On the one hand, the 22% prevalence of accommodative esotropia among parents and siblings clearly implies significant risk; on the other hand, approximately 75% of first-degree relatives are likely to be unaffected. Thus, although family history poses a significant risk, it must be evaluated in the context of other ophthalmic and sensory examination data. It should be noted that strabismus is a common condition (affecting 2%–4% of the population) and, in the absence of a control group, it is difficult to determine whether the prevalence of affected second- to fifth-degree relatives is significantly higher among patients with accommodative esotropia versus the general population.

Classification of family members as affected or unaffected in the pedigree analysis was accomplished with data gathered in directed interviews. Although ophthalmic examinations of all family members may appear at first glance to be a superior methodology, the disease of accommodative esotropia may be uniquely difficult to assess in this manner. In particular, accommodative esotropia that has been successfully treated during childhood may leave no detectable symptoms in adulthood. Neither esodeviation nor hyperopia may be present and binocular sensory function may be normal. Indeed, the interview approach that we used may have underestimated the prevalence of accommodative esotropia among relatives, since those who appeared to have other forms of strabismus or amblyopia or for whom insufficient detail was available regarding the character of the strabismic deviation, the age at onset of strabismus, or the type of treatment they received were not classified as affected.

The finding of subnormal random-dot stereopsis within a group of patients with recent diagnosis of intermittent accommodative esotropia suggests that, for at least some patients with accommodative esotropia, binocular sensory abnormalities may precede, and possibly contribute to, the onset of strabismus. This result is similar to results of two earlier studies of children with or at risk for accommodative esotropia which found that abnormal binocularity (fusion or stereopsis) precedes the onset of esotropia in some cases, but is not a necessary condition for the onset of esotropia.[2,20]

The increased risk for development of accommodative esotropia associated with anisometropia is particularly striking for children with lower amounts of hypermetropia. This suggests that screening for anisometropia among hypermetropic children may identify a subgroup which is at higher risk for development of accommodative esotropia than the overall group of hypermetropic children. Detection of anisometropia in children with hypermetropia < +4.00 D may provide an avenue for identifying those children who are at significant risk but would be missed if only spherical equivalent criteria were applied.

TABLE 3. Anisometropia and Relative Risk of Esotropia

Anisometropia	Relative Risk* of Esotropia (95% CI)
None (<1 D)	1.0
All patients (≥1 D)	1.68 (1.47–1.80)
≥1 D to <2 D	1.68 (1.42–1.82)
≥2 D	1.68 (1.31–1.85)

* Adjusted for significant baseline factors (age, mean spherical equivalent, and amblyopia).

TABLE 4. Anisometropia (≥1 D), Mean Spherical Equivalent, and Relative Risk of Esotropia

Mean Spherical Equivalent (SE) in Diopters (D)	Prevalence of Esotropia when Anisometropia Present (%) (n = 97)	Prevalence of Esotropia when Anisometropia Absent (%) (n = 248)	Relative Risk* of Esotropia with Anisometropia (95% CI)
All patients	87 (84/97)	51 (126/248)	1.68 (1.31–1.85)
Two Subgroups			
<3 D	92 (11/12)	12 (4/34)	7.79 (4.46–8.43)
≥3 D	86 (73/85)	57 (122/214)	1.49 (1.32–1.60)
1-D Subgroups			
2 to <3 D	92 (11/12)	12 (4/34)	7.79 (4.46–8.43)
≥3 to <4 D	81 (13/16)	38 (22/58)	2.14 (1.38–2.14)
≥4 to <5 D	89 (17/19)	73 (36/49)	1.22 (.86–1.33)
≥5 to <6 D	88 (23/26)	57 (24/42)	1.55 (1.16–1.69)
≥6 D	83 (20/24)	63 (39/65)	1.32 (.96–1.49)

* Adjusted for significant baseline factors (age, mean spherical equivalent, and amblyopia).

One caveat in the interpretation of the anisometropia data must be noted. As reported in the results section, there was a significant association between the presence of amblyopia and both anisometropia and esotropia. For the purpose of analysis of relative risk, amblyopia was not considered a baseline risk factor but rather was assumed to be an outcome of esotropia, anisometropia, or both. Nevertheless, even in nonamblyopic patients, anisometropia increased the RR for esotropia to 2.14, consistent with anisometropia as an independent risk factor. Moreover, from a practical standpoint, it may not matter whether the anisometropia or the amblyopia poses the greater risk for the development of accommodative esotropia. Given the high rate of co-occurrence, it may be simpler to screen for anisometropia than for amblyopia, particularly in preverbal children.

In conclusion, the present study identified positive family history, subnormal random-dot stereopsis before development of a constant deviation, and, in children with hypermetropia < +4.00 D, anisometropia as significant risk factors for the development of accommodative esotropia. Assessment of the presence or absence of these additional risk factors in conjunction with the overall amount of hypermetropia should help to identify those children who are most likely to benefit from preventive treatment before the onset of esotropia.

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