

LONG-TERM STUDY OF ACCOMMODATIVE ESOTROPIA

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ABSTRACT

Purpose: Previous studies of accommodative esotropia have been hampered by bias-prone methods of data collection and analysis and by small sample size. The studies have conflicting conclusions, causing uncertain results. This study aims to determine long-term results of standard treatment of accommodative esotropia and identify predictors of outcome, while minimizing bias in data collection and analysis, using the largest possible sample size.

Methods: A research assistant collected data from all files of a large, long-established pediatric ophthalmology practice (M.M.P.). The assistant was given standardized collection forms that allowed inclusion of all patient data points over all visits. The assistant was masked as to study goals. She was instructed to include any patient with esotropia who had been prescribed glasses during treatment. Descriptive terms were converted to code numbers. A second, similarly masked research assistant entered data into a computerized database. Criteria for patient inclusion were designed to conform to earlier studies by I.H.L. and M.M.P. and were implemented by computer.

Results: The database totaled 1,307 patients (747,717 data points). Of these, 354 qualified for this analysis. A greater difference between near and distance esodeviation (AC/A relationship) correlated with a higher rate of deterioration of accommodative esotropia control ($P < .0001$). Deterioration also positively correlated with earlier age at onset, inferior oblique overaction, and amblyopia.

Conclusions: This study agrees with our previous findings that a high AC/A relationship increases the likelihood of deterioration of accommodative esotropia, thus confirming the integrity of the database. This unique, unbiased dataset will be used for future analyses of esotropia.

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INTRODUCTION

Despite more than 135 years of experience and numerous studies and articles on the subject of accommodative esotropia, its treatment remains controversial. Agreed-upon diagnostic criteria and treatment regimens have yet to be established.

Published studies of accommodative esotropia have usually involved review of patient records by the practicing pediatric ophthalmologist, who then self-analyzed the data.¹⁻⁸ This method subjected these studies to potential

bias at a number of stages. Other studies have attempted a more objective approach by evaluating patients prospectively,⁹ but they are limited as to length of follow-up possible and are also subject to bias in patient selection and examiner testing.

After successful alignment of a child's eyes with spectacle correction, there remains a risk that the alignment control will deteriorate, requiring surgical correction to maintain alignment. Prior studies by two of the authors (I.H.L. and M.M.P.)^{1,2} evaluated the hypothesis that a higher rate of deterioration of accommodative esotropia occurred when the difference between the full cycloplegic refraction-corrected distance and near alignment in prism diopters (AC/A relationship) was high. The results showed a statistically significant correlation between deterioration rate and the AC/A relationship, but the study was hampered by small sample size (119 patients), which precluded testing of subgroups. Additionally, the data was collected by one of the authors (I.H.L.), who was cognizant of the hypothesis being tested, subjecting the study to potential bias.

A study was designed to fully utilize the data present

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in the large, long-established pediatric ophthalmology practice of one of the authors (M.M.P.), utilizing methods in data collection and analysis that would reduce bias to a minimum.

METHODS

A research assistant was hired to collect data from esotropia patients who had been seen in the private pediatric ophthalmology practice of Dr Marshall M. Parks. She had no prior ophthalmologic experience and was not informed about study goals or the earlier accommodative esotropia research. She was instructed to include all esotropic patients who were prescribed glasses at any time during treatment. The information was entered on specifically designed data collection forms. Descriptive terms were translated to numeric codes. All charts in Dr Parks' files were reviewed, and 1,307 were coded.

Dr Parks' examination and management protocol did not change over the 40 years of clinical practice covered by this study. Ocular alignment was obtained with prism, cover-uncover, and alternate cover measurement with accommodation control at 6 and 0.33 meters. Refractive state was determined by retinoscopy 40 minutes after instilling one drop of 2% cyclopentolate (combined with one drop of 1% tropicamide for darkly pigmented irides) on the anesthetized corneas.

At the LSU Eye Center, another research assistant entered the data into a computerized database. Records were identified by number only, protecting patient confidentiality. The data entry assistant was similarly masked as to study background or plan.

Data were sorted into separate data groups for each analysis by a nonmedical computer scientist (S.P.I.) and analyzed using the Statistical Analysis System (SAS Institute, Cary, NC) by a statistician (H.W.T.). Analyses of counts were conducted using an exact method for chi-square analysis.¹⁰ Continuous variables with two class levels were analyzed using the *t* test after checking the assumption of equality of variances and using the appropriate form of the *t* test.¹¹ In cases where multiple means were compared, the analysis of variance (ANOVA) was used with post hoc comparisons conducted after finding a significant overall F test for the ANOVA. The post hoc comparisons were conducted using the method of simulation-based multiple comparisons.¹²

Analysis for this study was designed to conform to the authors' previously published study¹ on accommodative esotropia. Criteria for inclusion in this study from the database were as follows:

1. Onset of esotropia prior to 8 years of age in a child having otherwise normal eyes
2. Alignment by spectacles alone to within 8 prism

diopeters (PD) for both distance and near viewing a. (The analysis was then repeated using all the same criteria, but with initial alignment within 4 PD.)

3. Minimum of 5 years of follow-up

Exclusion criteria were the following:

1. Anisometropia greater than 1.5 D spherical equivalent
2. Amblyopia of 20/100 or greater
3. Dissociated vertical deviation
4. Previous extraocular muscle surgery
5. Absence of follow-up within 2 years after receiving the initial spectacles
6. Mental retardation

The AC/A relationship (ratio) is defined according to the difference between the near and distance prism and alternate cover measurements. Less than 10 PD difference is considered within the range of normal, grade 1 high AC/A is a difference of 10 to 19 PD, grade 2 is 20 to 29 PD, and grade 3 is 30 PD or greater. The maximal AC/A ratio on the chart reviewed was used to grade the AC/A for each patient.

RESULTS

The database totaled 1,307 patients, with 747,717 data points. Of the 1,307 records in the database, 354 qualified for this study. Mean follow-up was 10.6 years (range, 5-42 years). Average age at onset was 2.7 years (range, 0-7.6 years). Bifocals were prescribed for 170 patients.

The study group was then reconfigured using all the same criteria, except the initial successful alignment with spectacles alone was defined as 4 PD or less, rather than 8 PD or less. The reason for this exercise is related to the criticism of the first study that 8 PD selected as a successful alignment status was excessive (Kenneth Wright, MD, oral communication, March 29, 2003). This reduced the study group size to 335. All tables summarizing the results compare the two criteria. Either of the two gives a similar trend.

Incidence of deterioration increased significantly with increasing AC/A grade ($\chi^2 = 27.37, P < .0001$) (Table I).

Mean AC/A averaged over all presurgical visits was 13.5 in the deteriorated group and 8.2 in the undeteriorated ($t = 5.1, P < .0001$). Mean AC/A averaged over all visits was 10.9 in the deteriorated group and 8.2 in the undeteriorated ($t = 3.1, P < .002$) (Table II).

As expected, incidence of bifocal use increased with increasing AC/A grade (Table III). Mean hyperopic spherical equivalent, averaged over all visits, was negatively correlated with AC/A grade ($P < .0001$), as was the maximal hyperopia recorded over all visits ($P < .0001$). Hyperopia recorded on each initial visit was also

TABLE I: DETERIORATION BY AC/A GRADE*

	NORMAL	GRADE 1	GRADE 2	GRADE 3	TOTAL
Deteriorated	35 (29)	40 (36)	46 (42)	56 (52)	177 (159)
Undeteriorated	67 (66)	52 (52)	31 (31)	27 (27)	177 (176)
Total	102 (95)	92 (88)	77 (73)	83 (79)	354 (335)

*Numbers indicate study group as initially defined. Numbers in parentheses indicate repeat analysis with study group limited to those with initial spectacle alignment to within 4 PD for both distance and near. Total numbers of patients may differ between tables due to missing values.

TABLE II: MEAN AC/A BY DETERIORATION STATUS*

	MEAN AC/A, ALL VISITS	SD	MEAN AC/A, PRESURGICAL	SD	NO.
Deteriorated	10.9 (11.2)	8.5 (8.7)	13.5 (13.8)	11.1 (11.5)	177 (159)
Undeteriorated	8.2 (8.2)	7.9 (7.9)	8.2 (8.2)	7.9 (7.9)	177 (176)

*Significance of numbers is explained in footnote to Table I.

TABLE III: BIFOCAL USE BY AC/A GRADE (NEAR DISTANCE PRISM COVER TEST)*

BIFOCAL PRESCRIBED	NORMAL	GRADE 1	GRADE 2	GRADE 3	TOTAL
Yes	4 (4)	39 (36)	72 (67)	74 (72)	188 (179)
No	98 (91)	53 (52)	6 (6)	9 (7)	166 (156)
Total	102 (95)	92 (88)	77 (73)	83 (79)	354 (335)

*Significance of numbers is explained in footnote to Table I.

negatively correlated with AC/A grade ($P < .0001$) (Table IV).

Mean delay-to-treatment (as per parental history) was not significantly different between the deteriorated and undeteriorated groups (Table V). Incidence of amblyopia was significantly higher in the deteriorated group than the undeteriorated group (Table VI).

Inferior oblique overaction was strongly correlated with deterioration (Table VII) ($P = .0005$), but inferior oblique overaction at initial examination (Table VIII) was not significantly higher in the deteriorated groups. Mean age at onset was significantly lower in the deteriorated than the undeteriorated groups ($P < .0001$) (Table IX). Time to deterioration (following initial spectacle alignment) was compared by AC/A grade and did not show significant differences (Table X).

DISCUSSION

This study agrees with our previous findings that a high AC/A relationship increases the likelihood of deteriora-

tion of accommodative esotropia, thus confirming the integrity of the database.¹ The other findings from the earlier study,¹ which are also confirmed here, were the lesser hypermetropia associated with greater AC/A grade and the earlier age at onset in the deteriorated group. The significant associations between amblyopia and deterioration, and maximum inferior oblique overaction and deterioration, seen in this study were not demonstrated in our original study.¹ This difference may be explainable by the greater sample size of this database.

Other studies have examined the rate of deterioration of accommodative esotropia as correlated to the AC/A relationship or ratio. Von Noorden and associates⁵ found a higher rate of deterioration when the AC/A ratio was low, but their study measured the gradient AC/A ratio. Another study using gradient AC/A found no correlation to deterioration.⁶ The gradient AC/A measures the near alignment response to incremental addition of plus lenses. A child whose excessive near convergence responds poorly to additional plus correction would have a low

TABLE IV: MEAN HYPERMETROPIA BY AC/A GRADE (ANOVA)^o

HYPEROPIA	NORMAL	GRADE 1	GRADE 2	GRADE 3
Mean hyperopia, all visits	3.67 (3.83)	3.25 (3.32)	2.34 (2.32)	2.26 (2.29)
Maximum hyperopia	4.38 (4.54)	4.03 (4.11)	3.21 (3.2)	3.45 (3.49)
Hyperopia, initial visit	3.62 (3.77)	3.05 (3.11)	2.3 (2.29)	2.2 (2.2)

^oSignificance of numbers is explained in footnote to Table I.

TABLE V: DELAY-TO-TREATMENT^o

	MEAN DELAY-TO-TREATMENT (MO)	SD	NO.
Deteriorated	7.9 (7.5)	13.6 (11.9)	129 (116)
Undeteriorated	7.3 (7.2)	14.3 (12.5)	115 (115)

^oSignificance of numbers is explained in footnote to Table I.

TABLE VI: AMBLYOPIA VERSUS DETERIORATION^o

	AMBLYOPIA PRESENT	AMBLYOPIA ABSENT	TOTAL
Deteriorated	65 (53)	67 (62)	132 (115)
Undeteriorated	42 (41)	89 (89)	131 (130)
Total	107 (94)	156 (151)	

^oSignificance of numbers is explained in footnote to Table I.

TABLE VII: MAXIMUM INFERIOR OBLIQUE OVERACTION, ALL VISITS^o

	NORMAL	1+10	2+10	3+10	TOTAL
Deteriorated	104 (93)	25 (22)	21 (19)	26 (24)	176 (158)
Undeteriorated	139 (138)	11 (11)	15 (15)	11 (11)	176 (175)
Total	243 (231)	36 (33)	36 (34)	37 (35)	352 (333)

^oSignificance of numbers is explained in footnote to Table I.

AC/A ratio by the gradient method but may have a high distance-near relationship, rendering these studies noncomparable to studies of the distance-near relationship.

Raab³ reported a 13% rate of deterioration in accommodative esotropes with normal AC/A relationships and a 21% rate in those with high AC/A relationships. The differences were not statistically significant. The smaller

sample size of his study, and possibly shorter mean follow-up, may account for the lack of statistical significance.

Our finding of increasing hypermetropia with decreasing AC/A grade was reported by other investigators.^{3,4,13} Also, the increased risk of deterioration with earlier onset of accommodative esotropia, as demonstrated here, is consistent with other reports.^{4,6}

Delay-to-treatment was not shown to significantly

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TABLE VIII: INFERIOR OBLIQUE OVERACTION, INITIAL VISIT^o

	NORMAL	1+IO	2+IO	3+IO	TOTAL
Deteriorated	149	10	3	0	162
Undeteriorated	149	7	6	2	164
Total	298	17	9	2	326

^oSignificance of numbers is explained in footnote to Table I.

TABLE IX: AGE AT ONSET^o

	MEAN AGE AT ONSET	SD	TOTAL
Deteriorated	2.44 yr (2.41 yr)	1.3 (1.3)	151 (137)
Undeteriorated	3.01 yr (2.98 yr)	1.3 (1.3)	146 (145)

^oSignificance of numbers is explained in footnote to Table I.

TABLE X: TIME TO DETERIORATION^o

	NORMAL	GRADE 1	GRADE 2	GRADE 3
Deteriorated	13.2 mo (14.3)	18.4 mo (19.0)	20.1 mo (21.2)	20.2 mo (21.2)

^oSignificance of numbers is explained in footnote to Table I.

impact the risk of deterioration, but the study group included only cases in which patients were initially successfully aligned with spectacles alone. Excessive delay would presumably cause early deterioration and prevent initial spectacle alignment, eliminating the case from this study group.

This study analyzes a small subset of the larger database of esotropia patients. These results serve the dual purposes of supporting our earlier work and the integrity of this complex database. This database now promises the unique opportunity to study and compare other groups of esotropia patients and other parameters of all the patients. Our initial impression after trying to group these cases is that esotropia patients are a more complex and heterogeneous population than is generally appreciated. From this large, long-term practice (M.M.P.), all patients with esotropia and glasses are included in the database and await study.

The use of unbiased data collection and data entry personnel is unique in this study. Data analysis required defining parameters precisely and programming the computer to sort the patients into the subgroups. This prevents bias in diagnosis, for example. Prospective following of patients confers no reduction of bias in a study if the examiners are not masked as to study goals or

patient status. A clinical trial of an intervention requires diagnosis of a disorder, random assignment of an intervention or control treatment, and prospective, masked following of the patient for a defined period of time.¹⁴ The value of spectacles in treatment of some esotropia patients is not in doubt, but the natural history of these patients over time is subject to speculation. There is disagreement over diagnostic criteria for accommodative esotropia, need for bifocals in cases with high AC/A, timing of surgery, and other measures. The long-term nature of these problems would render a classic clinical trial unfeasible. Although limited, short-term questions (such as the recent successful trial comparing efficacy of atropine in amblyopia treatment) can be addressed with a clinical trial, the multiple questions still remaining in esotropia treatment would require a long-term cohort study, akin to the Framingham Heart Study.¹⁵ The effort and expense would be prohibitive.

The patients in this database represent all esotropia patients treated with glasses by a single pediatric ophthalmologist in private practice during a period of more than 50 years. Each visit is documented on the record, always typed, and presented in a consistent format. Although this database was necessarily collected using retrospective data, methods were employed to minimize bias in data

collection and analysis, and the patient care was delivered before this study was envisioned. These factors should reduce bias to the minimum level possible within reasonable limits of time and expense.

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DISCUSSION

DR J. BRONWYN BATEMAN. Doctors Ludwig, Parks and their colleagues have taken advantage of a superb database of one of our esteemed members who has set the 'gold standard' in pediatric ophthalmology and strabismus. These authors have codified all patients with pediatric esotropia controlled with glasses and treated by a single provider. They defined "control" and alignment within 4 prism diopters with glasses and required a minimum of 5 years follow-up. Although the data was collected with minimal biases, the individual reviewing the charts was not a practitioner. Using this data, the authors have asked the following question: Are there statistically useful predictive factors for the maintenance of alignment with corrective lenses?

Although retrospective, this database has significant potential for answering questions that have been debated for many years. Those of us who have worked with Dr Parks can attest his remarkable consistency with management techniques. The large numbers of patients increase the power of the analyses. Although confounding variables remain, the authors have relatively narrow inclusion criteria. The follow-up period is relatively long and the data collection is relatively consistent reducing biases.

What conclusions are reasonable from this study? Nearly 50% of patients with accommodative esotropia required bifocals for entry into the study. The higher the AC/A ratio, the more likely the patient cannot be controlled with glasses. Inferior oblique over-action correlated with deterioration but is not a predictive parameter.

I have several suggestions for consideration. The authors should define 'deterioration' as precisely as possible. The power of the analyses should be assessed. They may wish to reassess the grading of AC/A ratio; the standard deviation of the measurement may require broader categories. Amblyopia is a confounding factor and may warrant analysis if there is sufficient power. The authors may wish to use more complex statistical analyses such as discriminant or logistic regression analyses. Lastly, I would make the same caution that Dr Ed Stone made yesterday – if you do enough analyses, by chance, you will come up with a statistically significant result.

Lastly, I wish to congratulate Drs Ludwig and Parks as well as their colleagues. Dr Parks has a very valuable database in his office. Once records are computerized, a very young ophthalmologist, undoubtedly not yet an AOS member, may be presenting a prospective study 60 years from now.

DR ARTHUR JAMPOLSKY. I want to congratulate the authors for calling our attention once again to the teaching of Donders 100 years ago to the nuances of any hyperopia or

any residual uncorrected hyperopia, causing an esodeviation. The author's study was motivated by the bias of previous studies and the stated method was to eliminate or minimize the biases. The standard treatment is what I would like to see defined. What was defined was the 1.5 diopters of anisometropia that was corrected but there was no minimum degree of hyperopia correction that was implemented as part of the standard treatment. What was the minimum degree of hyperopia? Was it prescribed as a full prescription? How long used, compliance, and at what stage?

It was also stated that the selection criteria included anyone who was prescribed glasses during this study. Perhaps the full data display will bring out whether the full prescription was prescribed, or a partial correction, and the effect upon the deviation. I feel sure that the full display of the large amount of data accumulated in this important study will allow one to ascertain whether some residual uncorrected hyperopia could be responsible for many of the high accommodative-convergence relationships described.

You know, we all have biases. The other person's biases are called prejudices. One's own biases are called principles. My principles include a full optical correction beginning at 2 diopters of hyperopia at any age. Perhaps your data will compare these to your principles?

DR KENNETH W. WRIGHT. The paper was on accommodative esotropia, but accommodative esotropia is probably not just one disease, it's multi-factorial. Some infantile or congenital ET's were thrown in here that happen to be hypermetropic. With that background, it was interesting that patients with inferior oblique overaction had a higher of deterioration, is that right?

Perhaps those patients were really congenital or infantile esotropes? Inferior oblique overaction manifests itself later. Was there a correlation with onset of the esotropia and deterioration? Those that have early onset had a tendency to deteriorate. Was there a correlation between inferior oblique overaction and those with early onset?

DR EDWARD L. RAAB. It is not necessarily the initial hypermetropia that is found, but the rate at which it progresses. I'm sure you've got that information if you've got all those data points and I wonder if you could address that question.

DR IRENE H. LUDWIG. In response to Dr Bateman's comments, further statistics and other methods of analyzing this data are definitely being planned including advanced methods, such as data mining. The purpose of this report was to duplicate our original study and provide it additional power. That is all we did for this subset, and

why we chose these statistical methods.

As for Dr Jampolsky's question, most patients had full hyperopic correction, but I have not specifically analyzed your question in this study. The entire database includes 1,307 patients, but the cases I reported today are the 354 who were aligned initially by spectacles alone. There are many other patients in the larger database that we have not yet studied. We have a wealth of information and many more analyses to perform. Glasses in the large database were prescribed at any time during treatment. I did not want to limit the data collector, and just instructed her to include esotropic patients who had received glasses at any time. The group of patients I reported today are the ones that received glasses early on and were fully successfully aligned with the glasses alone.

We did find correlation between earlier age of onset and higher rate of deterioration. The age of onset versus inferior oblique overaction has not been studied. At the time of deterioration, there was a higher rate of inferior oblique overaction, but not initially. We also haven't studied stereopsis results but that data is available and another study to perform. Rate of hyperopia progression and the long-term hyperopic results of all these patients is a very interesting study that we plan to pursue.

