



Refractive Growth of the Crystalline Lens in the Infant Aphakia Treatment Study

Thaddeus S. McClatchey, MD,^{1,2} Scott R. Lambert, MD,³ David G. Morrison, MD,⁴ Stacey J. Kruger, MD,⁵ Lorri B. Wilson, MD,⁶ Scott K. McClatchey, MD,^{2,7} for the Infant Aphakia Treatment Study Group*

Objective: To compare the rate of refractive growth (RRG3) of the crystalline lens (“lens”) versus the eye excluding the lens (“globe”) for the fellow, noncataractous eyes of participants in the Infant Aphakia Treatment Study.

Design: Retrospective cohort study.

Subjects: A total of 114 children who had unilateral cataract surgery as infants were recruited. Biometric and refraction data were obtained from the normal eyes at surgery and at 1, 5, and 10 years. Subjects were included if complete data (axial length [AL], corneal power, and refraction) were available at surgery and at 10 years of age.

Methods: At surgery and at 1, 5, and 10 years, AL, corneal power, and cycloplegic refraction were measured in the normal eyes. For each eye, the RRG3 was defined by linear regression of refraction at the intraocular lens (IOL) plane against $\log_{10}(\text{age} + 0.6 \text{ years})$. The RRG3 for the globe was based on IOL power for emmetropia; the RRG3 for the lens was based on IOL power calculated to give the observed refractions. Intraocular lens powers were calculated with the Holladay 1 formula. The means were compared with a paired 2-tailed *t* test, and linear regression was used to look for a correlation between RRG3 of the lens and globe.

Main Outcome Measures: The RRG3 of the lens and globe.

Results: Complete data were available for 107 normal eyes. The mean RRG3 of the lenses was -12.0 ± 2.5 diopters (D) and the mean RRG3 of the globes was -14.1 ± 2.7 D ($P < 0.001$). The RRG3 of the lens correlated with the RRG3 of the globe ($R^2 = 0.25$, $P < 0.001$).

Conclusions: The RRG3 was 2 D more negative in globes compared with lenses in normal eyes. Globes with a greater rate of growth tended to have lenses with a greater rate of growth. *Ophthalmology Science* 2022;2:100208 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at www.ophtalmologyscience.org.

The normal crystalline lens changes throughout childhood, with a reduction in optical power as the front and back surface curves flatten and the thickness and refractive index change. The eye excluding the lens can be considered an aphakic eye, with an effective refraction that is hyperopic and becomes less hyperopic as the axial length (AL) changes. Hereafter, we will use the terms “lens” for “crystalline lens” and “globe” for the “eye excluding the lens.” The reduction in the positive power of the lens closely matches the reduction in the hyperopic refractive error due to increasing AL, which maintains the entire eye in a nearly constant refractive state.¹ The lessening power of the lens with increasing age has previously been evaluated in a cross-sectional study where children having a variety of ocular surgeries had biometric and refraction measurements that allowed calculation of the intraocular lens (IOL) power that would be required to give the observed refractions.² Other studies have been performed longitudinally, demonstrating changes in refractive index, shape, and thickness of the lens with age.^{3–6}

Refractive changes of both the lens and globe are nonlinear. Just as the nonlinear Snellen visual acuity may be

converted to the logarithm of the minimum angle of resolution for statistical analysis under the assumption of linearity, the nonlinear growth metrics of the eye can also undergo a linear transformation for analysis and comparison.

The eyes of children after cataract surgery have a refractive error that is nonlinear and follows a semi-logarithmic curve. The relationship between refractive error (at the plane of the IOL) and age (adjusted for the in utero growth of the eye by adding 0.6 years⁷) in aphakic or pseudophakic eyes is semilogarithmic from infancy to 20 years.^{8,9} The slope of this line is characteristic for each eye, termed “rate of refractive growth” (RRG3),⁹ and is independent of age at surgery and the length of follow-up. The RRG3 has proven useful in analyzing factors that might influence the myopic shift of a growing eye¹⁰ and in predicting future refractive error for pseudophakic eyes.^{7,11} Just as the RRG3 of the globe (RRG3_{globe}) can be calculated based on biometric measurements at different ages,¹⁰ an analogous RRG3 can be calculated for the lens (RRG3_{lens}) based on longitudinal measurements of

Table 1. Values for Refraction, AL, and Corneal Power of the 107 Included Normal, Nonsurgical Eyes at Surgery and at 1, 5, and 10 Years

Age group	Age (yrs)	Refraction (D)	AL (mm)	Corneal Power (D)
Surgery	0.19 ± 0.14	2.44 ± 1.84	18.54 ± 0.89	45.49 ± 1.87
1 yr	0.90 ± 0.04	1.48 ± 1.46	20.69 ± 0.66	43.16 ± 1.55
5 yrs	4.98 ± 0.08	1.64 ± 1.41	22.11 ± 0.78	43.28 ± 1.57
10 yrs	10.61 ± 0.26	0.26 ± 2.20	23.37 ± 1.00	43.18 ± 1.56

Values are reported as value ± standard deviation. AL = axial length; D = diopters.

biometry and refraction. The RRG3 of the globe and RRG3_{lens} are separate and distinctly calculated rates, with units of diopters (D) (Equations 1, 2). For the purposes of this study, the RRG3 can be defined by linear regression of refraction at the IOL plane against the log of (age + 0.6 years). The RRG3 of the globe was based on IOL power for emmetropia; RRG3_{lens} was based on IOL power calculated to give the observed refractions. For precise calculation of RRG3, it is best to have measurements taken in infancy and again many years later because the uncertainty in the value of RRG3 due to errors in measurements is least when the line segment in the semilogarithmic plot is long.

The Infant Aphakia Treatment Study (IATS) prospectively studied 114 children who had unilateral cataract surgery as infants, with or without IOL implantation.¹² Most of these patients had longitudinal biometric data from the normal nonsurgical eye obtained at surgery and at 1, 5, and 10 years of age. These data can be used for the calculation of RRG3_{globe} and RRG3_{lens}.

Pediatric eyes tend to become less hyperopic with age, which could be attributed to a mismatch between the

RRG3_{lens} and RRG3_{globe}. In addition, because the components of the eye tend to grow together, it is possible that increased axial elongation (as shown by RRG3_{globe}) could correspond to a greater reduction in the lens power (as shown by RRG3_{lens}).

Our primary hypothesis was that the mean RRG3_{lens} is less than the mean RRG3_{globe}. This would result in a net myopic shift of these normal eyes, on average. Our secondary hypothesis was that RRG3_{lens} correlates with RRG3_{globe}.

Methods

This study was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health and was conducted at 12 clinical sites. This study was approved by the institutional review boards at all participating institutions and was in compliance with the Health Insurance Portability and Accountability Act. [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00212134. The analysis in this substudy was approved as a Quality Improvement project, NMCS.D.QI.2020.111601. This study adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

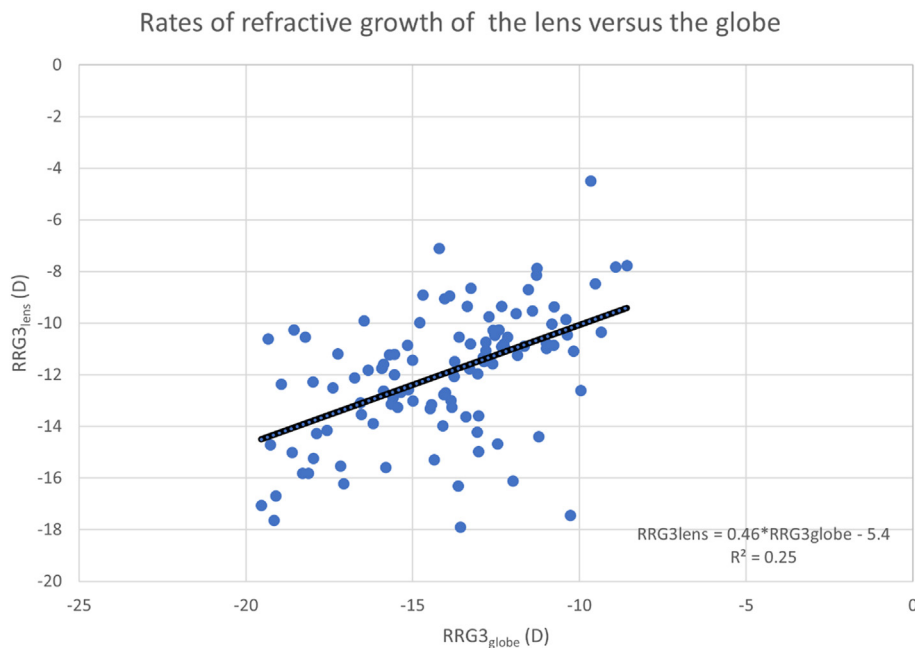


Figure 1. Rate of refractive growth of the normal lens versus RRG3 of the globe. The coefficient of determination (R^2) = 0.25, indicating a weak correlation between these values. The greater the RRG3 of the globe, the greater the RRG3 of the lens. D = diopters; RRG3 = rate of refractive growth.

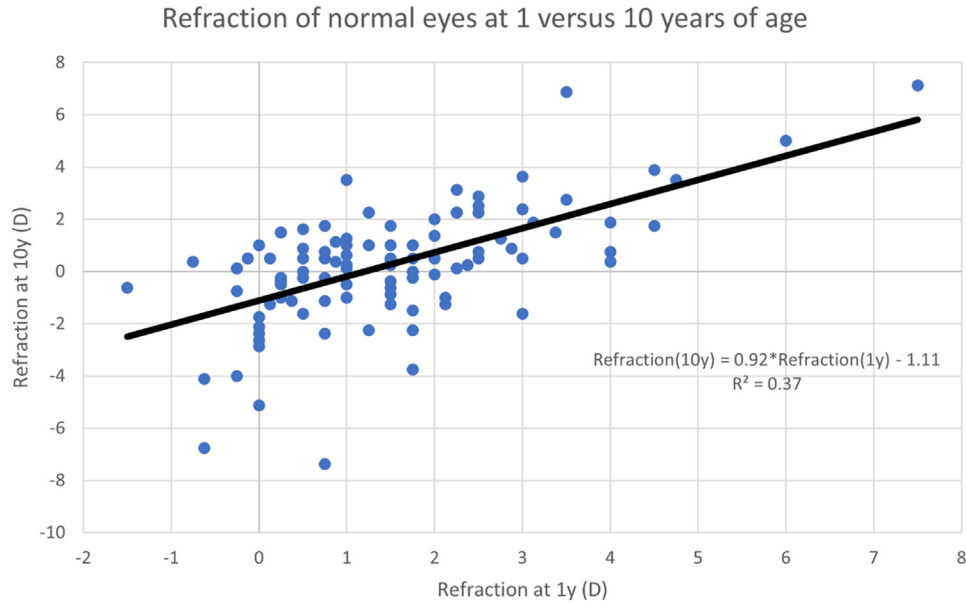


Figure 2. Refraction at 1 year versus 10 years of age. Of the 71 eyes with a refraction of < +2 D at age 1 year, 38% were myopic, with a refraction of < -0.5 D at age 10 years, compared with 9% of the 35 eyes with refraction \geq +2 D at age 1 year. D = diopters.

Study Design

The main inclusion criteria were a visually significant infantile onset cataract (≥ 3 mm central opacity) in 1 eye, a normal nonsurgical eye, and an age of 28 to < 210 days at the time of cataract surgery. The main exclusion criteria for the IATS were an acquired cataract, persistent fetal vasculature causing stretching of the ciliary processes, or a corneal diameter of < 9 mm.¹² For this substudy, we included only the nonsurgical normal eyes that had complete data (age, AL, corneal power, and refraction) at surgery and at the 10.5-year (hereafter abbreviated 10-year) examination.

Surgical Technique and Optical Correction

The details of the randomization, surgical technique, and optical correction have been described previously.¹²

Clinical Examinations

Biometric data for the normal eyes were obtained at the time of cataract surgery and at ages 1, 5, and 10 years, including cycloplegic refraction, AL and corneal power. When possible, autorefractometry was performed. If an autorefractometry could not be performed, retinoscopy was used to perform the refraction.

One child was found to have Stickler syndrome and was subsequently excluded from the analysis.

Calculation of RRG3

The RRG3 of the globe was based on IOL power for emmetropia; RRG3_{globe} was based on IOL power calculated to give the observed refractions (Equations 1, 2). Intraocular lens power was calculated using the Holladay 1 formula. For the purposes of our study, we used all available data points from the examinations at surgery and at 1, 5, and 10 years of age and calculated the RRG3 for each eye using linear regression of IOL power versus \log_{10} (age + 0.6 years).

Statistical Analysis

The Shapiro-Wilk Royston test was used to demonstrate normality, a 2-sided paired *t* test was used to compare means, and linear regression was used to look for a correlation between RRG3_{lens} and RRG3_{globe}. Because multiple comparisons were made and because this study is one of many post hoc analyses of the IATS data, only *P* values of < 0.001 were considered significant.

Equations

$$RRG3_{globe} = \frac{IOL_{final} - IOL_{initial}}{\log_{10}(age_{final} + 0.6 \text{ years}) - \log_{10}(age_{initial} + 0.6 \text{ years})}$$

Equation 1. This formula defines RRG3_{globe}. IOL_{final} and IOL_{initial} are defined as the IOL powers required for emmetropia at the final examination and at the time of surgery, respectively. Age_{final} and age_{initial} are defined as the patient's ages at the final examination and at the time of surgery, respectively. The addition of 0.6 years is to correct for the in utero growth of the eye. Because $(\log[a] - \log[b])$ is equivalent to $\log(a/b)$, the unit of the denominator cancels out, and RRG3 has units of D. For the purposes of this study, linear regression was used to calculate RRG3 from the 4 available data points.

$$RRG3_{lens} = \frac{Lens_{final} - Lens_{initial}}{\log_{10}(age_{final} + 0.6 \text{ years}) - \log_{10}(age_{initial} + 0.6 \text{ years})}$$

Equation 2. This formula defines the RRG3_{lens}. Lens_{final} and Lens_{initial} are defined as the IOL powers required for the observed refraction at the final examination and at the time of surgery, respectively. Age_{final} and age_{initial} are defined as the patient's ages at the final examination and at the time of surgery, respectively. The addition of 0.6 years is to correct for the in utero growth of the eye. Because $(\log[a] - \log[b])$ is equivalent to $\log(a/b)$, the unit of the denominator cancels out, and RRG3 has units of D. For the purposes of this study, linear regression was used to calculate RRG3 from the 4 available data points.

Table 2. Comparison between Change in AL and K from the Study by Mutti et al³ from 9 Months to 4.5 Years of Age and the IATS Study from 1 to 5 Years of Age

Study	Δ Age (yrs)	Δ AL (mm)	Δ K (D)
Mutti et al ³	4.13 \pm 0.03	1.67 \pm 0.07	-0.5 \pm 0.14
IATS	4.09 \pm 0.08	1.47 \pm 0.04	0.00 \pm 0.98

Δ Age, Δ AL, and Δ K refer to change in AL and K over the specified period. The IATS data include those 88 eyes that met the inclusion criteria for our study and had complete data available at the 1- and 5-year examinations. Values are reported as value \pm standard deviation.

AL = axial length; D = diopters; IATS = Infant Aphakia Treatment Study; K = corneal power.

Results

Biometric and refraction data were available for 107 normal nonsurgical eyes both at surgery and at 10 years of age. In addition, complete data were available for most of these eyes at the 1-year (n = 99) and 5-year (n = 94) examinations. Values at all examinations for refraction, AL, and corneal power are listed in Table 1.

The mean $RRG3_{lens}$ was -12.0 ± 2.5 D, and the mean $RRG3_{globe}$ was -14.1 ± 2.7 D (P [same means] < 0.001, 2-sided paired t test). In linear regression analysis, the $RRG3_{lens}$ was correlated with $RRG3_{globe}$ ($R^2 = 0.25$) (Fig 1).

The mean power of the lens was $+35.8 \pm 3.8$ D at the time of surgery of the cataractous eye and $+21.5 \pm 1.8$ D at age 10 years.

We also observed that the refraction at age 1 year was correlated with the refraction at age 10 years ($R^2 = 0.37$, P [correlation] < 0.001, F-significance via analysis of variance) (Fig 2) for the 106 eyes that had refractions at ages 1 and 10 years. Of the 71 eyes with a refraction of < +2 D at age 1 year, 38% were myopic, with a refraction of < -0.5 D at age 10 years, compared with 9% of the 35 eyes with refraction $\geq +2$ D at age 1 year.

Discussion

The mean $RRG3$ was 2 D more negative for the globe than for the lens. For these normal nonsurgical eyes, this resulted in an average net myopic shift.

We hypothesized that the lens refractive change would be proportionate to the growth of the rest of the eye, that is, the $RRG3$ of the normal lens would correlate with the $RRG3$ changes of the globe. Indeed, 25% of the difference in $RRG3_{lens}$ could be explained by variance in $RRG3_{globe}$: the

eyes that grew faster (greater $RRG3_{globe}$) had a greater rate of growth of the lens (greater $RRG3_{lens}$). These results are consistent with our secondary hypotheses.

Incidental to the main purpose of our study, we also found that the refraction at age 1 year was correlated with refraction at age 10 years, with the age 1 refraction explaining 37% of the age 10 refraction. Eyes that were initially less hyperopic (refraction < +2 D at age 1 year) were > 4 times as likely to be myopic at the age of 10 years compared with more hyperopic refractions at the age of 1 year. This suggests the possibility of early intervention; a future study could examine whether an intervention to slow the progression of myopia (such as daily, low-concentration atropine drops) starting at the age of 1 year could lessen the long-term rate of myopia.

The authors of this paper previously analyzed $RRG3$ in this same data set and found that the standard deviation of $RRG3$ of normal nonsurgical globes was half that of the eyes that underwent cataract surgery.¹¹ We extend this work by calculating the $RRG3$ for the lens itself and comparing it with the $RRG3$ of the globe.

Mutti et al³ fit the changing lens power to a polynomial curve similar to the semilogarithmic curve of the $RRG3$ model, based on longitudinal data from normal children aged 0.25 to 6.5 years. The pattern of refractive growth for our data set followed a similar logarithmic model. Mutti et al³ also described change in AL and keratometry from 0.25 to 6.5 years. These results are compared with those of our study in Table 2. Although the studies are similar, a statistical comparison is difficult because the closest age data match inexactly: 9 months to 4.5 years for Mutti et al³ versus 1 year to 5 years for the IATS.

Our study is limited in that the “normal” eyes examined in this study were the paired nonsurgical eyes of infants who underwent unilateral cataract surgery. Thus, these eyes may vary at baseline from the general population who did not develop a unilateral cataract in infancy. Further, these infants underwent patching therapy of the normal nonsurgical eye, which might affect the growth of this eye and confound our results.

We believe that the method used to assess the refractive power growth of the lens, by converting it to the linear form of $RRG3$, can be used in future clinical studies that analyze the growth of the lens or AL. In this way, the confounding effects of age at measurement and length of follow-up can be eliminated. This is analogous to the conversion of the nonlinear Snellen visual acuity to the linear form of the logarithm of the minimum angle of resolution, which is now understood to be necessary for statistical analysis of visual acuity.

Footnotes and Disclosures

Originally received: March 6, 2022.

Final revision: August 2, 2022.

Accepted: August 2, 2022.

Available online: August 7, 2022. Manuscript no. XOPS-D-22-00040.

¹ Department of Ophthalmology, Naval Medical Center, San Diego, California.

² School of Medicine, California University of Science and Medicine, San Bernardino, California.

³ Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, California.

⁴ Department of Ophthalmology and Visual Sciences, Vanderbilt University Medical Center, Nashville, Tennessee.

⁵ Department of Ophthalmology, Northwell Health, Bethpage, New York.

⁶ Casey Eye Institute, Oregon Health & Science University, Portland, Oregon.

⁷ Department of Surgery, Uniformed Services University of Health Sciences, Bethesda, Maryland.

*See [Appendix](#) for the Infant Aphakia Treatment Study Group.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors have made the following disclosures: S.R.L.: Financial support – National Eye Institute.

S.K.M.: Employee – US Government. This work was prepared as part of his official duties. Title 17, USC §105 provides that “Copyright protection under this title is not available for any work of the United States Government.” Title 17, USC §101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person’s official duties.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

Supported by National Institutes of Health (grants U10 EY13272, U10 EY013287, UG1 EY013272, UG1 EY025553, and P30 EY026877), Research to Prevent Blindness, Inc, and the Norm Medow Foundation.

Presented in part at the AAPOS meeting, April 9-11, 2021, virtual.

HUMAN SUBJECTS: Human subjects were included in this study. Institutional review board approval was obtained at all participating institutions. All research adhered to the tenets of the Declaration of Helsinki. All information presented in this study is HIPAA-compliant. All participants provided informed consent.

No animals subjects were used in this study.

Author Contributions:

Conception and design: TS McClatchey, Lambert, SK McClatchey

Data collection: TS McClatchey, Lambert, Morrison, Kruger, Wilson, SK McClatchey

Analysis and interpretation: TS McClatchey, Lambert, SK McClatchey

Obtained funding: N/A

Overall responsibility: TS McClatchey, Lambert, Kruger, Wilson, SK McClatchey

Abbreviations and Acronyms:

AL = axial length; **D** = diopters; **IOL** = intraocular lens; **RRG3** = rate of refractive growth.

Keywords:

IATS, Ocular development, Pediatric cataract surgery, RRG3.

Correspondence:

Scott K. McClatchey, MD, 34800 Bob Wilson Drive, San Diego, CA 92134. E-mail: scott.k.mcclatchey.civ@mail.mil.

References

1. Zadnik K, Mutti DO, Mitchell GL, et al. Normal eye growth in emmetropic schoolchildren. *Optom Vis Sci.* 2004;81: 819–828.
2. Gordon RA, Donzis PB. Refractive development of the human eye. *Arch Ophthalmol.* 1985;103:785–789.
3. Mutti DO, Sinnott LT, Lynn Mitchell G, et al. Ocular component development during infancy and early childhood. *Optom Vis Sci.* 2018;95:976–985.
4. Fledelius HC, Christensen AS, Fledelius C. Juvenile eye growth, when completed? An evaluation based on IOL-Master axial length data, cross-sectional and longitudinal. *Acta Ophthalmol.* 2014;92:259–264.
5. Zadnik K, Mutti DO, Fusaro RE, Adams AJ. Longitudinal evidence of crystalline lens thinning in children. *Invest Ophthalmol Vis Sci.* 1995;36:1581–1587.
6. Mutti DO, Mitchell GL, Sinnott LT, et al. Corneal and crystalline lens dimensions before and after myopia onset. *Optom Vis Sci.* 2012;89:251–262.
7. McClatchey SK, Hofmeister EM. The optics of aphakic and pseudophakic eyes in childhood. *Surv Ophthalmol.* 2010;55: 174–182.
8. McClatchey SK, Parks MM. Myopic shift after cataract removal in childhood. *J Pediatr Ophthalmol Strabismus.* 1997;34:88–95.
9. Whitmer S, Xu A, McClatchey S. Reanalysis of refractive growth in pediatric pseudophakia and aphakia. *J AAPOS.* 2013;17:153–157.
10. McClatchey SK, McClatchey TS, Cotsonis G, et al. Refractive growth variability in the Infant Aphakia Treatment Study. *J Cataract Refract Surg.* 2021;47:512–515.
11. McClatchey SK. Intraocular lens calculator for childhood cataracts. *J Cataract Refract Surg.* 1998;24:1125–1129.
12. Infant Aphakia Treatment Study Group, Lambert SR, Buckley EG, et al. The Infant Aphakia Treatment Study: design and clinical measures at enrollment. *Arch Ophthalmol.* 2010;128:21–27.