Risk Factors for Progressive Myopia in the Atropine Therapy for Myopia Study

KAI-LYN LOH, QINGSHU LU, DONALD TAN, AND AUDREY CHIA

• PURPOSE: To investigate variables associated with myopic progression despite treatment in the Atropine in the Treatment of Myopia Study.
• DESIGN: Retrospective cohort study.
• METHODS: Two hundred of 400 children were randomized to receive atropine 1% in 1 eye only in this institutional study. Children were followed up with cycloplegic autorefraction every 4 months over 2 years. Children whose myopia progressed by more than 0.5 diopter (D) in the atropine-treated eye at 1 year were classified as being progressors.
• RESULTS: Among the 182 children still in the study at 1 year, 22 (12.1%) were classified as progressors. Univariate analysis suggested these children tended to be younger (8.5 ± 1.4 years vs 9.3 ± 1.5 years; $P = .023$), to have higher myopic spherical equivalent (SE) at baseline (−3.6 ± 1.3 D vs −2.8 ± 1.4 D; $P = .015$), and to have 2 myopic parents (77.3% vs 48.1%; $P = .012$). In nonprogressors, the myopia progression at 1 year was less in the atropine-treated eyes compared with the untreated fellow eye (+0.16 ± 0.37 D vs −0.73 ± 0.48 D; $P < .001$), but in progressors, progression was more similar between eyes (−0.92 ± 0.31 D vs −1.06 ± 0.44 D; $P = .363$). Regression analysis showed that the risk of being a progressor was 40% lower with each year of increased age, 43% lower for every 1.0 D less in myopia at baseline, and 59% lower for every 1.0 D less in myopic change in the untreated eyes over the first year.
• CONCLUSIONS: Doctors and parents need to be aware that there is a small group of children (younger, with higher myopia, and greater tendency of myopic progression) who may still progress while receiving atropine treatment. (Am J Ophthalmol 2015;■:■–■.

Accepted for publication Jan 26, 2015.

From the Singapore National Eye Center, Singapore (K.-L.L., D.T., A.C.); the Singapore Clinical Research Institute, Singapore (Q.L.); the Center for Quantitative Medicine, Duke-National University of Singapore Graduate Medical School, Singapore (Q.L.); the Singapore Eye Research Institute, Singapore (D.T., A.C.); and the Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (D.T.).

Inquiries to Audrey Chia, Singapore National Eye Center, 11 Third Hospital Avenue, Singapore 168751; e-mail: wla_chia@yahoo.com

THE INCREASING PREVALENCE OF MYOPIA WORLDwide, and particularly in East Asia, has spurred the research and clinical interest in the control of myopic progression. The impetus included the wish to decrease the myopic burden to individuals and society and also to reduce the risk of potentially blinding complications associated with high myopia.[1] Atropine has been shown to be quite effective in slowing myopia progression in many studies.[2–6] In the Atropine for the Treatment of Childhood Myopia (ATOM) 1 study, topical atropine 1% therapy was shown to slow myopic progression by 80% at 2 years compared with control eyes (−0.28 ± 0.92 diopters [D] vs −1.20 ± 0.68 D; $P \leq .001$).[7] Similar findings have been described in other studies. However, in previous studies, as well as clinically, there are some children who showed progressive myopia despite treatment with atropine.[7,8] The aim of this study was to investigate the risk factors in children who recorded myopia progression despite treatment with atropine 1% in the ATOM 1 study.

METHODS

THE STUDY PROTOCOL WAS IN ACCORDANCE WITH THE principles of the Declaration of Helsinki and was approved by the Singapore Eye Research Institute Review Board. Written informed consent was given by parents or legal guardians of the children before enrolment. This was a retrospective cohort study based on the data from the ATOM 1 study. The ATOM 1 study was a prospective, randomized, double-masked, placebo-controlled trial of 400 children between 6 and 12 years of age with low to moderate myopia.

Participants were randomized into 2 groups: an atropine-treatment group and a placebo-treatment group. Only data from children in the atropine group were used for analysis in this study. In this group, children received atropine 1% in 1 randomly assigned eye and vehicle agent (0.5% hydroxypropyl methylcellulose and 1:10 000 benzalkonium chloride) in the other eye. Children were reviewed at a pretreatment visit, then 2 weeks after treatment was started (baseline), and then every 4 months for 2 years. Cycloplegic autorefraction and axial length were measured at each visit.

Cycloplegic autorefraction was performed by investigators who were trained in study protocols and was performed

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2015.01.029

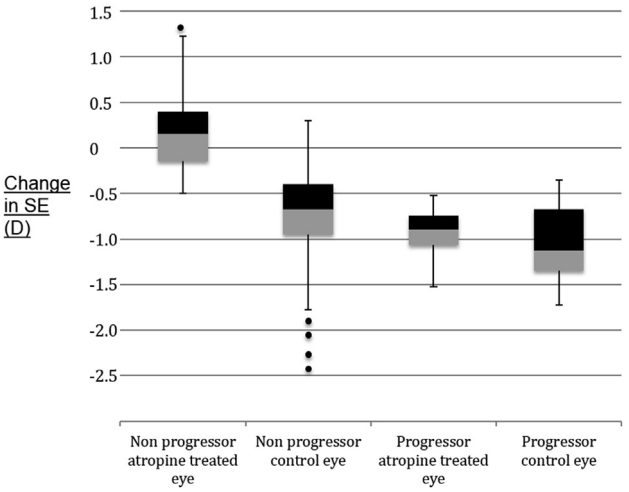

FIGURE 1. Box-and-whisker plot comparing myopia progression in both progressors and nonprogressors treated with 1% atropine. D = diopters; SE = spherical equivalent.

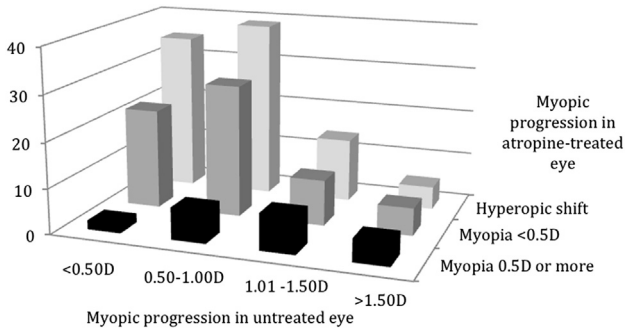

FIGURE 2. Bar graph comparing myopia progression in atropine-treated eyes according to myopia progression in the control eye. D = diopters.

to assess refractive errors at baseline and then every 4 months in the first year of the study. The cycloplegic regimen used included 1 drop of proparacaine hydrochloride (Alcaine; Alcon-Couvreur, Puurs, Belgium) followed by 3 drops of 1% cyclopentolate hydrochloride (Cyclogyl; Alcon-Couvreur) timed 5 minutes apart. Cycloplegic autorefraction measurements were obtained 30 minutes after the last drop using a Canon RK5 autorefractor-autokeratometer (Canon, Inc, Ltd, Tochigiken, Japan); 5 readings with a maximum difference of 0.25 D were recorded and averaged. Spherical equivalent was calculated as sphere plus half cylinder power. Axial length measures were assessed by A-scan ultrasonography with Nidek US-800 EchoScan (Nidek, Co, Ltd, Tokyo, Japan): 6 readings were recorded and averaged (with standard deviation of 0.12 mm).

Parents also completed a questionnaire at baseline visit that contained questions on patients' social history such as housing type, number of hours spent on homework, type of homework, outdoor activities and hobbies. Parental myopia data also were collected, but this was based on parent self-report.

• **STATISTICAL ANALYSIS:** Children with myopia progression of more than 0.50 D at 1 year in the atropine-treated eye were classified as being progressors because this value was clinically significant. The progressors and nonprogressors were compared with regard to baseline characteristics (such as age, gender, and spherical equivalent [SE]), change in SE at 1 year from baseline, as well as the socioeconomic and myopia status of their parents. Potential risk factors, that is, those with a P value of less than .10 in the comparison between progressors and nonprogressors, were included in the log-binomial model to assess their association with the risk of progressive myopia.

RESULTS

ONE HUNDRED EIGHTY-TWO (91.0%) OF THE INITIAL 200 PARticipants in the atropine-treated group were still in the study at 1 year. Twenty-two children (12.1%) had myopic progression of more than 0.5 D in the first year and were classified as progressors. In these children, there was a mean myopic progression of −0.92 ± 0.31 D in the atropine-treated eye compared with −1.06 ± 0.44 D in the untreated eye (P = .363; Figure 1). In contrast, nonprogressors had a mean hyperopic shift of +0.16 ± 0.37 D at 1 year in the atropine-treated eye, compared with −0.73 ± 0.48 D in the untreated eye (P < .001). Over 2 years, there was a mean myopic progression of −1.25 ± 0.68 D in the treated eyes of the progressors versus −0.15 ± 0.84 D in those of the nonprogressors.

Only 2% (n = 1) of children who progressed by less than 0.50 D in untreated eye were progressors, compared with 9% (8), 24% (8) and 31% (5) in those who progressed 0.50 to 1.00 D, 1.01 to 1.50 D, and more than 1.50 D in the untreated eyes, respectively (Figure 2). Compared with nonprogressors, progressors were younger (8.5 ± 1.4 years vs 9.3 ± 1.5 years; P = .023; Table 1), started to wear spectacles at a younger age (6.7 ± 1.2 years vs 7.3 ± 1.5 years; P = .066), and were more myopic at baseline (−3.6 ± 1.3 D vs −2.8 ± 1.4 D; P = .015). The mean change of SE in the first year was greater in the progressor group than in the nonprogressor group in both the treated eyes (−0.92 ± 0.31 D vs +0.16 ± 0.37 D; P < .001) and the untreated eyes (−1.06 ± 0.44 D vs −0.73 ± 0.48 D; P = .003). The 2 groups of children were comparable with regard to age at first spectacle prescription and in the distribution of gender and ethnicity (Table 1). No significant differences were found between the progressors and the nonprogressors regarding time spent on outdoor activities

TABLE 1. Comparison of Demographics and Other Characteristics between Myopic Nonprogressors and Progressors in Atropine-Treated Eyes

	Nonprogressors (n = 160)	Progressors (n = 22)	*P* Value
Change in SE (D) over 1 y, mean (SD)[a]			
Atropine-treated eye	0.16 (0.37)	−0.92 (0.31)	<.001
Fellow untreated eye	−0.73 (0.48)	−1.06 (0.44)	.003
Change in SE (D) over 2 y, mean (SD)[b]			
Atropine-treated eye	−0.15 (0.84)	−1.25 (0.68)	<.001
Fellow untreated eye	−1.17 (0.66)	−1.53 (0.65)	.049
Male gender, no. (%)	89 (55.6)	13 (59.1)	.822
Chinese ethnicity, no. (%)	155 (96.9)	20 (90.9)	.201
Age at baseline (y), mean (SD)	9.3 (1.5)	8.5 (1.4)	.023
Age spectacle wear began (y), mean (SD)	7.3 (1.5)	6.7 (1.2)	.066
SE at baseline (D), mean (SD)	−2.8 (1.4)	−3.6 (1.3)	.015
First spectacle prescription (D), mean (SD)	1.46 (0.83)	1.50 (0.57)	.881
Parental myopia status, no. (%)			
Mother with myopia	118 (73.8)	20 (90.9)	.111
Father with myopia	104 (65.0)	19 (86.4)	.055
Both parents with myopia	77 (48.1)	17 (77.3)	.012
Mother's education level, no. (%)			
Primary/secondary education	75 (46.7)	9 (40.9)	.234
Preuniversity or diploma	40 (25.0)	7 (31.8)	
Tertiary	44 (27.5)	6 (27.3)	
Father's education level, no. (%)			
Primary/secondary education	52 (32.5)	6 (27.3)	.978
Preuniversity or diploma	38 (23.8)	6 (27.3)	
Tertiary	67 (41.9)	10 (45.5)	
Housing type, no. (%)			
3- or 4-room HDB flat	28 (17.5)	2 (9.1)	.657
5-room flat/HDB maisonette	63 (39.4)	9 (40.9)	
Private housing	67 (41.9)	11 (50.0)	

D = diopters; HDB = Housing Development Board (government-subsidized housing); SD = standard deviation; SE = spherical equivalent.
[a]Change from baseline to 1 year.
[b]Change from baseline to 2 years. Note that at 2 years, the number of nonprogressors was 154 and the number of progressors was 16.

(6.1 ± 4.1 hours per week vs 5.9 ± 4.9 hours per week; $P = .877$) and various near-work activities, such as time spent reading or writing, watching TV, or playing video games.

The prevalence of myopia in parents was higher among progressors compared with nonprogressors. Among the progressors, 90.9% of mothers, 86.4% of fathers, 77.3% of both parents had myopia, compared with 73.8% ($P = .111$), 65.0% ($P = .055$), and 48.1% ($P = .012$), respectively, among the nonprogressors (Table 1). There were, however, no differences in parental education levels or socioeconomic status (as defined by housing type) between groups.

Multiple log-binomial regression analysis was performed on selected parameters, including parental myopia, age at baseline, age when the child started to wear spectacles, myopia at baseline, and progression of myopia in the untreated fellow eye. The adjusted analysis showed that the risk of progressive myopia decreased by 59% for every 1.0 D less change in SE in the untreated eye (Table 2). Similarly, there was a 41% lower risk of progressive myopia with every year of increasing age. SE at baseline had a relative risk of 0.57, meaning that for every 1.0 D less myopia at baseline, the risk of progressive myopia was 43% lower. Conversely, the risk of progressive myopia was 165% higher if both parents were myopic than if otherwise. Age when children started to wear spectacles became less significant after adjustment for other parameters.

DISCUSSION

THE ATOM 1 STUDY CONFIRMED THAT TOPICAL 1.0% ATROPINE results in clinically significant reduction of myopia progression in childhood.[7] However, 1.0% atropine causes pupil dilation and decreased accommodation, so that children started on bilateral treatment will require tinted glasses and reading add to cope with the glare and blur of

TABLE 2. Regression Analysis of Risk Factors for Progressive Myopia Despite Treatment with 1% Atropine

Variable	Unadjusted Analysis		Adjusted Analysis	
	Relative Risk (95% Confidence Interval)	*P* Value	Relative Risk (95% Confidence Interval)	*P* Value
Change in SE (untreated eye)[a]	0.40 (0.22 to 0.71)	.002	0.41 (0.19 to 0.88)	.022
Age at baseline	0.73 (0.56 to 0.96)	.023	0.59 (0.39 to 0.91)	.017
Age when spectacles first worn	0.78 (0.60 to 1.01)	.061	1.14 (0.75 to 1.73)	.550
SE at baseline	0.71 (0.54 to 0.94)	.018	0.57 (0.42 to 0.78)	<.001
Both parents with myopia	3.15 (1.21 to 8.17)	.018	2.65 (1.07 to 6.59)	.036

SE = spherical equivalent.
[a]Change from baseline to 1 year.

near vision.[7] It is also known that sudden cessation of atropine 1% after 2 years can result in a myopic rebound.[9] In the current study, we further noted that 12.1% of children progressed (by more than 0.5 D over the first year) despite topical atropine 1.0% treatment. These progressors tended to be younger, to have higher myopia at baseline, to have parents with myopia, and to have greater progression of myopia in the untreated fellow eye. These factors seem suggest that these children may have a greater inherent tendency for myopia progression and were less responsive to the effects of atropine. Nonbiological factors such as hours of near and distance work seemed to be less relevant, suggesting that atropine perhaps may work in a way that mitigates the environmental factors that induce myopia progression.[10]

Rapid myopia progression despite atropine treatment has been described in other studies. In the ATOM 2 study, where children were randomized to atropine concentrations of 0.5%, 0.1%, and 0.01%, 18% of children in all 3 cohorts recorded a progression of 0.5 D or more in the first year.[11] Shih and associates, in a study monitoring effect of 0.5% atropine and multifocal over 18 months, noted that 7 (10.6%) of 66 patients showed progression of 0.75 D or more.[12] In a study of differing atropine concentrations, Shih and associates found that 4%, 17%, and 33% of the children in the 0.5%, 0.25%, and 0.1% atropine groups, respectively, showed myopia progression of more than −1.0 D per year.[13]

Wu and associates, in a study examining 0.05% atropine use in Taiwanese children, noted that 19 (20%) of 97 children in the treatment group had more than 0.5 D of myopia progression per year.[8] In an analysis of the fast progressors, they found that higher initial SE corresponded significantly to a higher chance of myopia progression despite atropine. Age and gender were not found to be significant factors.

The underlying reasons why these children did not respond as well (eg, whether there were genetic factors or different mechanisms that drove myopia in these individuals) is uncertain and needs further exploration, although the earlier age of onset, higher degree of myopia, and more rapid myopia progression in the nontreated eyes in these progressors suggest that the effect of atropine simply was inadequate on control progression in these children with more severe myopia. A detailed review of children's treatment diaries suggest that in 4 of the 22 children who were progressors, compliance was not optimal. However, although progression occurred, this did not mean there was no response. Among the 22 progressors, myopia progression was still less rapid in the atropine-treated eye compared with the fellow untreated eye by more than 0.5 D in 7 children, suggesting that the true nonresponse rate to atropine 1% may be closer to 7%. We are not aware of any studies that have evaluated even higher concentrations of atropine eyedrops beyond 1%, and it is interesting to speculate about whether the dose-response effect of atropine could be useful in these high progressors if higher doses of atropine were to be tested clinically, although then the potential for more side effects with a higher dose would need to be assessed.

Clinically, the results of the ATOM 1 study suggest that most children (91%) will respond to atropine 1% in the first year. Our study suggested that a small group of children (range, 7% to 12%) with a possible greater inherent risk will still progress, despite atropine treatment. However, before treatment, it is difficult to predict who these children will be, and indeed this may not be determined until approximately 6 to 12 months into treatment. Under study conditions, we were able to compare this response with that of the fellow untreated eye to gauge if there was no response or a smaller response. In the clinical setting where children are often treated bilaterally, we may not be certain of the effect of atropine 1% (ie, some or none). However, if myopia progression continues at a rate similar to that before the start of atropine treatment, then one could assume that atropine is ineffective and should be stopped.

In this study, we looked at myopia progression in children on the highest 1.0% atropine dose. However, the more recent trend is to treat children with lower doses of atropine, and the response profile in these children may be different.[11] It could be presumed that children who do not respond to 1.0% atropine also will not respond to lower doses of atropine. It is important that clinicians are aware of this fact and that parents be counselled appropriately.

Strengths of this study include its randomized double-blind design involving a large number of subjects with a low rate of loss to follow-up. Because atropine was assigned randomly to only 1 eye, it was possible to monitor the natural myopia progression in the individual by observing the change in the other eye. Although there may be some concern regarding a systemic effect of treatment in one eye versus the other, the findings from our previous studies suggest otherwise, with progression in the fellow eye being very similar to that in placebo eyes.[7,9]

Limitations of the study include having only studied the patients receiving the 1.0% atropine concentration, where the absolute number of progressors was small. It is uncertain if there are other confounding factors (eg, specific environmental or compliance rates) that might have influenced response. Overall, however, there were no gross differences in hours spent indoors and outdoors. Compliance in the group of progressors generally was good in most of the children, but was suboptimal in 4 children (18%). There also could be other genetic or social factors that might have escaped consideration in the planning of the study.

This study adds more insight into the clinical response of myopic children to atropine treatment. In the small group of children (younger, the children of parents with myopia, and predisposed naturally to higher progression of myopia), rapid progression despite atropine treatment may warrant a review of the need for continuing atropine treatment and an exploration of other myopia control treatment options.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported. Supported by Grant MH 95:03/1-23 from the National Medical Research Council, Singapore, and Grant SHF/FG039/2004 and TEST 08-03 from SingHealth, Singapore. Involved in Design and conduct of study (A.C., D.T.); Collection (A.C., D.T.), management (A.C., D.T.), and analysis and interpretation (K.-L.L., Q.S., D.T., A.C.) of data; and Preparation, review, and approval of manuscript (K.-L.L., Q.S., D.T., A.C.).

REFERENCES

1. Gilmartin B. Myopia: precedents for research in the twenty-first century. *Clin Experiment Ophthalmol* 2004;32(3):305–324.
2. Bedrossian RH. The effect of atropine on myopia. *Ophthalmology* 1979;86(5):713–719.
3. Dyer JA. Role of cycloplegics in progressive myopia. *Ophthalmology* 1979;86(5):692–694.
4. Brodstein RS, Brodstein DE, Olson RJ, Hunt SC, Williams RR. The treatment of myopia with atropine and bifocals. A long-term prospective study. *Ophthalmology* 1984;91(11):1373–1379.
5. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol* 1989;21(5):180–182,187.
6. Saw SM, Gazzard G, Eong KA, Tan DTH. Myopia: attempts to arrest progression. *Br J Ophthalmol* 2002;86(11):1306–1311.
7. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. *Ophthalmology* 2006;113(12):2285–2291.
8. Wu PC, Yang YH, Fang PC. The long-term results of using low-concentration atropine eye drops for controlling myopia progression in schoolchildren. *J Ocul Pharmacol Ther* 2001;27(5):461–466.
9. Tong L, Huang XL, Koh AL, Zhang X, Tan DT, Chua WH. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology* 2009;116(3):572–579.
10. Saw SM. A synopsis of the prevalence rates and environmental risk factors for myopia. *Clin Exp Optom* 2003;86(5):289–294.
11. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). *Ophthalmology* 2012;119(2):347–354.
12. Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT, Lin LLK. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand* 2001;79(3):233–236.
13. Shih YF, Chen CH, Chou AC, Ho TC, Lin LLK, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther* 1999;15(1):85–90.