Original Article

Refractive and ocular biometric profile of children with a history of laser treatment for retinopathy of prematurity

Savleen Kaur, Jaspreet Sukhija, Deeksha Katoch, Mansi Sharma, Ramanuj Samanta, Mangat R Dogra

Purpose: Indian children belong to a diverse socioeconomic strata with retinopathy of prematurity (ROP) developing in mature, higher birth weight babies as well. The purpose of our study is to analyze the long-term status of refractive errors and its relationship with ocular biometry in children with ROP who were laser treated at a tertiary center in North India. **Methods:** Cross sectional study. Children (<16 years) enrolled from January 2014 to December 2014 with a history of laser treatment for ROP and examined for refractive and biometric status. **Results:** Thirty-six children presenting to us at the mean age of 7.37 ± 3.07 years (6–15 years) were included. Mean spherical equivalent (SE) was −4.05 D ± 5.10. 75% were myopic, with high astigmatism in 31%. Higher lens thickness (P = 0.03) and higher SE (P = 0.002) at 1 year postnatal age were predictors of larger SE. 79.4% achieved a favorable functional outcome (visual acuity ≥20/40). 5.88% achieved unsatisfactory outcome (<20/200) despite having a favorable structural outcome. **Conclusion:** There are a substantial number of children who develop myopia and high astigmatism while undergoing laser treatment for ROP. We found myopia in our cohort to be lenticular and greater axial length contributing to the development of high myopia. An initial large refractive error predicts the future development of myopia in these children. Nearly 6% of patients with good structural outcome have unexplained subnormal vision. Our threshold for prescribing glasses in these children should be low.

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Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative disease seen in premature infants. Almost 50,000 children up to the age of 15 years are blind from ROP worldwide.[1,2] Confluent laser photocoagulation is a highly effective therapy for ROP. However, morbidity and burden of ROP do not end with laser photocoagulation. Despite a successful anatomic outcome following laser photocoagulation, these children have the risk of developing refractive errors, strabismus, and amblyopia which may result in suboptimal visual outcomes.[3,4] The Early Treatment for ROP Cooperative Group (ETROP) study reported nearly 60% of those efficiently treated have suboptimal vision (<20/60) and up to 29% of treated children develop severe visual impairment (worse than 20/200).[5]

Myopia is the most common refractive error in babies who have been treated for ROP with laser photocoagulation.[6-9] The prevalence of myopia in premature babies with or without ROP is reported to vary between 21% and 100%.[7-11] The cause of myopia and its anatomic correlates in these eyes is still to be adequately answered.[8,11,12] Reports have linked myopia in children with ROP to prematurity, severe ROP and structural sequelae of laser treatment.[9] Understanding the mechanism behind the development and progression of refractive errors in children with ROP who have undergone laser photocoagulation is crucial to developing appropriate management tools as well as counseling of parents regarding refractive error development and progression after laser photocoagulation.

It is well known that heavier and more mature babies develop severe forms of ROP including Aggressive Posterior ROP (APROP) in a developing country like India.[13-16] The profile of ROP in these children seems to be different from those in the West. Hence, we need to identify the changes in the ocular biometric profile of these children treated with laser photocoagulation for ROP. This would help us in determining the development and progression of refractive error in these eyes.

Methods

This study was conducted at a tertiary care referral institute. The study adhered to the Declaration of Helsinki. A review of the charts of all children who visited the pediatric ophthalmology clinic between January 2014 and December 2014 with a history of laser treatment for ROP was done. We excluded patients who had spontaneous regression/underwent surgery/received bevacizumab for ROP. Patients with secondary pathologies like glaucoma or cataract (except strabismus) were also excluded. Patients with any other systemic disease were excluded. The records were reviewed for gestational age and birth weight. The

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highest stage of ROP achieved/presence of APROP was noted. The children who needed treatment were either threshold ROP (cryotherapy for ROP)/type 1 prethreshold ROP/APROP in accordance with ETROP guidelines.[17] The time it took for regression of disease and refractive error at follow-up visits was also noted. The refractive error measured on a subjective streak retinoscopy after the ROP regressed; at any time between 10 and 12 months of age was substituted as the retinoscopy value at 1 year of age when the refraction at 1 year was not available.

At presentation, we examined for visual acuity, strabismus, and/or amblyopia. The refractive error was measured by streak retinoscopy after dilation with cyclopentolate 1% (three times at an interval of 10 min) by a certified optometrist. Visual acuity was measured on Snellen chart at 6 m in children who cooperated and by LEA SYMBOLS in younger children and then converted to logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. Contrast sensitivity (CS) was assessed using Pelli Robson chart at 1 m. The last triplet from which the child identified at least two of the three letters correctly was converted to log contrast value. The biometric profile including the axial length (AL), keratometry (K), and anterior chamber depth (ACD) was measured on the intraocular lens master (Carl Zeiss Jena, Germany). Lens thickness (LT) was measured on the A scan (Tomey AL-100 Biometer). All the biometric values were taken after cycloplegia. Eyes were preanesthetized with 0.5% proparacaine and probes were gently placed on cornea without indenting during A scan. The average of the three best readings was taken. The central macular thickness (CMT) was measured on spectral-domain optical coherence tomography (OCT) in children who could cooperate. Posterior segment was examined with indirect ophthalmoscopy and a 20 D lens for structural sequelae (in the form of narrowing of arcades/straightening of vessels/disc drag/macular heterotropia/retinal detachment/fold involving fovea/corneal opacity).

The primary outcome measures were present visual acuity, spherical equivalent (SE), and the average myopic shift/year. SE was measured as spherical error + half cylindrical error. Myopia was defined as SE ≤–0.5 D; high myopia >6 D and hyperopia >0.5 D. Astigmatism more than 2 D was classified as high astigmatism. It was further classified into with the rule (75°–105°), against the rule (0°–15° and 165°–180°) and oblique (16°–74°/106°–164°). Anisometropia was defined as >1.5 D difference in SE in two eyes. The average myopic shift/year was defined as the difference between the SEs at the present examination and the SE at 1 year of age divided by the age. Overall visual outcome was defined as good if the visual acuity was better than or equal to 20/40, satisfactory if between 20/40 and 20/200 and suboptimal if visual acuity was worse than 20/200.

Statistical analysis

Nonparametric tests on SPSS Version 21 (SPSS; IBM SPSS Statistics for windows, version 21.0. Armonk, NY, USA) were done for statistics. Spearman's correlations were done to determine the correlation between continuous data variables. Regression analysis was used to see the effect of variables such as birth weight, gestational age, zone of the disease, the presence of APROP, and biometric parameters on the outcome measures. Subgroup analysis was performed by *t*-test. As two eyes of the same patient may behave different structurally after laser treatment, they were considered as independent variables. $P < 0.05$ was considered significant.

Results

Thirty-six children (72 laser-treated eyes) who presented to us at the mean age of 7.37 ± 3.07 years (range 6–15 years) were included after obtaining informed parental consent. All patients had undergone laser photocoagulation for ROP in both the eyes previously. There were 24 males (66.6%) and 12 females (33.3%).

The mean gestational age in weeks at the time of birth was 29.01 ± 2.2 and the mean birth weight in grams was 1262 ± 32.7. Zone I involvement was present in 26 (37.1%) and Zone II in the rest 10. APROP was present in 13 (36.1%) and plus disease in all patients. Mean postmenstrual age at which the treatment was performed was 35.6 ± 1.7 weeks. Seventeen patients (47.2%) had laser treatment with diode laser (510 nm) and rest with green laser (532 nm). Time taken for the disease to show signs of regression after laser treatment ranged from 7 to 30 days (median 14 days). Supplemental laser therapy session was needed in two eyes. There was no patient with family history of high myopia.

Overall favorable structural outcome was seen in 94.4%. Structural sequelae developed in 4 eyes. One developed macular heterotopia and 3 had narrowing of the temporal vascular arcades. None of the patients had retinal detachment.

Visual acuity and refractive error

At presentation, the mean visual acuity on LogMAR was 0.29 ± 0.57 (20/63 approximately [ranging from 20/200 to 20/20 could be measured on Snellen in all children]). Visual acuity was better than 20/40 in 54 eyes (75%); 20/40–20/200 in 10 eyes (13.8%) and worse than 20/200 in 8 eyes (11.2%). All the four eyes which developed structural sequelae had visual acuity of <20/200. There were 4 eyes who had low vision (<20/200) without strabismus or anisometropia. The SE in these eyes ranged from −2.5 to −4 D with cylinder 0.5–1.0 D. The mean CS was 1.28 log CS units. Mean SE was −4.05 ± 5.10 D (ranging from 1 D to −13.5 D). Twenty-seven patients were myopic (54 eyes; 75%), 7 had hyperopia (14 eyes; 20%), and 2 had negligible refractive error (SE 0.5 D). Out of these, 35 eyes had myopia >4 D and 19 eyes had myopia > 6 D.

The mean astigmatism measured in the negative cylinder was −1.2 ± 1.21 DC, and with the rule, astigmatism was present in 78.8%. Eleven patients (22 eyes; 30.5%) developed high astigmatism. Eight children had an anisometropia (22.2%).

From the initial refraction at 1 year of age, the mean myopic change was −2.7 ± 7.07 D ($P = 0.04$) in these children and the average myopic shift/year was − 0.41 ± 1.0 D [Fig. 1]. The change in mean cylinder was − 0.34 ± 0.99 D and average change in cylinder/year was − 0.05 ± 0.23 D. Distribution of refractive error in these children at different time points is shown in Table 1. The percentage of children with high astigmatism and myopia was similar at all age points. Those who had high myopia at 1 year of age continued to have high myopia in later life also. CMT was 315.4 ± 36.11 microns in the 14 children who had a clear OCT scan. Lesser CMT ($r = −0.5$; $P < 0.000$), larger SE ($r = 0.49$; $P = 0.018$), and a low gestational age at birth (($r = −0.2$; $P = 0.0$) were predictors for a poor visual acuity. Hence, lower gestational age preterm babies tended to have a significantly lesser visual acuity and more

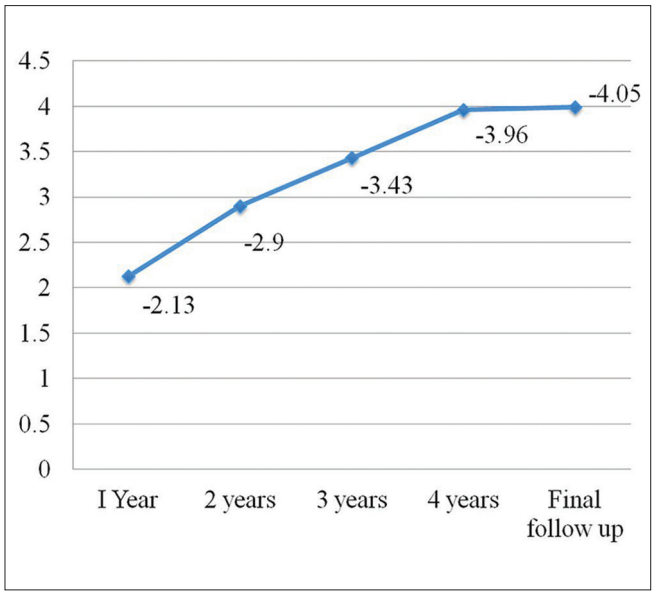

Figure 1: The change in mean spherical equivalent in diopters with time

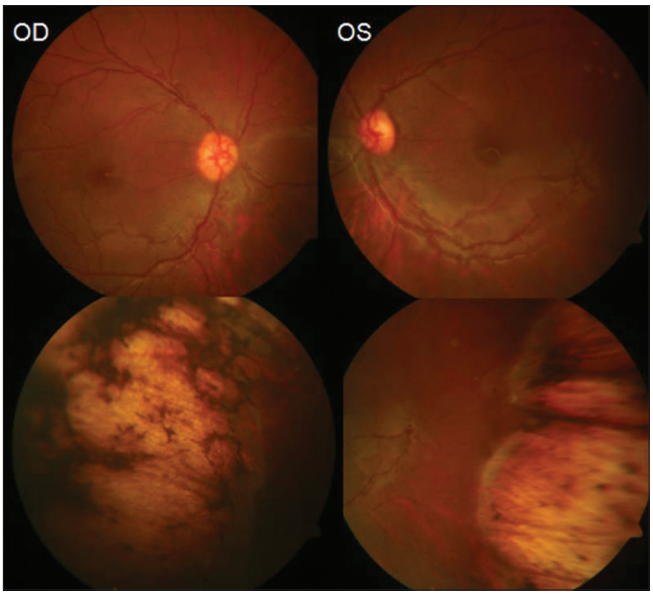

Figure 2: Fundus picture of a 6-year child lasered for aggressive posterior retinopathy of prematurity. Visual acuity is 20/30 right eye (−8.75 D) and 20/30 left eye (−6 D)

myopia. The gestational age at the time of laser, birth weight and stage of disease did not affect the visual acuity ($P = 0.08$, 0.383, 0.54 and 0.123 respectively). Involvement of zone 1 and APROP was associated with a greater myopic shift ($P = 0.001$ and 0.039) but did not affect the absolute value of the SE. Astigmatism was not influenced by the zone of ROP or plus disease.

Strabismus and amblyopia

There was strabismus in 11 (30.5%; six had esotropia and five exotropia more than 8 PD) and amblyopia in 10 (27.7%). Three had strabismic, three had anisometropic amblyopia, and four had bilateral ametropic amblyopia (Amblyopia defined as best-corrected visual acuity <20/40 in one or both the eyes without any structural pathology or sequelae in these children). The anisometropia ranged from 3 to 6 D. In only one out of the three patients with anisometropia, there were asymmetric structural sequelae that corroborated with the findings of anisometropia. The other two patients had greater AL as well as LT in the eyes with more refractive error than the contralateral eyes.

Correlation of biometric variables

The mean value of the various ocular biometric components as well as the correlation between gestational age, birth weight, and various optical parameters is given in Table 2. There was no correlation between prematurity status and any of the biometric parameters. Higher LT ($P = 0.03$) and higher SE ($P = 0.002$) at 1-year postnatal age were predictors of poorer outcome (in terms of greater SE). We also studied the biometric variables of children with low, high, or no myopia [Table 3]. We found out that the children with high myopia had statistically significant greater LT ($P = 0.006$) and AL ($P = 0.05$) than the others. There was no statistical difference in the keratometry and ACD or the myopic shift in these eyes.

Out of those 94.4% with favorable structural outcome, 79.4% achieved a good functional outcome with visual acuity >20/40, 14.7% achieved a satisfactory outcome and 5.88% achieved unsatisfactory outcome (visual acuity <20/200) [Fig. 2].

Table 1: Distribution of refractive error in the postnatal age

Refractive status	Postnatal age	Percentage of children
Anisometropia ≥0.5 D	1 year	72
	2 years	78.6
	3 years	70.6
	4 years	69.2
	Last follow-up	64.4
Anisometropia ≥2 D	1 year	24
	2 years	21.4
	3 years	29.4
	4 years	38.5
	Last follow-up	35.6
Myopia ≥4 D	1 year	54
	2 years	48
	3 years	50.6
	4 years	56.3
	Last follow-up	48.6

Discussion

The study presents the long-term status of refractive errors and its relationship with biometric components in children with ROP, who are laser treated, after a mean age of 7 years. It is a well-known fact that preterm children have higher rates of myopia and more so if they develop severe ROP requiring treatment.[7-10] Since the infants affected with severe ROP are on the rise with the third epidemic of the same,[18] soon there will be more children affected by myopia. The load of refractive errors and amblyopia will rise. Long-term function in these children is determined by the burden of refractive errors. Early recognition of refractive errors is therefore important leading to timely intervention for the refractive amblyopia these children might develop.

Table 2: Correlation analysis of gestational age and birth weight with refractive and biometric components

	Mean	Gestational age	Birth weight
Visual acuity			
LogMAR	0.29±0.57	*r*=−0.2* *P*=0.02	*r*=0.25
Refraction			
Spherical equivalent (D)	−4.05±5.10	*r*=0.3* *P*=0.00	*r*=0.075
Astigmatism (D)	−1.2±1.21	*r*=−0.021	*r*=−0.056
Mean myopic shift/year	−0.41±1.0	*r*=0.048	*r*=0.137
Mean change in cylinder/year	−0.05±0.22	*r*=0.105	*r*=−0.154
Biometric components with range			
Corneal refractive power (D)	45.8±1.89 (41.1-51.74)	*r*=−0.21	*r*=−0.236
Axial length (mm)	20.35±1.65 (18.18-26.91)	*r*=0.206	*r*=0.125
Lens thickness (mm)	4.33±0.35 (3.01-5.05)	*r*=0.001	*r*=0.026
Anterior chamber depth (mm)	2.95±0.47 (2.0-4.69)	*r*=0.112	*r*=0.030
Corneal thickness (μ)	541±43.6	*r*=0.030	*r*=0.034
Central macular thickness (μ)	315.4±36.11	*r*=0.112	*r*=0.045

LogMAR: Logarithm of the minimum angle of resolution. * Significant *P* value; *P*<0.05

Table 3: Relationship of refractive and biometric variables between patients with no myopia, low myopia, and high myopia

	No myopia or hyperopia (*n*=18)	Mild to moderate myopia ≥0.5 D-6 D (*n*=35)	High myopia ≥6 D (*n*=19)	*P*
Axial length (mm)	20.96±0.72	20.95±1.8	21.42±1.27	0.054
Anterior chamber depth (mm)	3.13±0.325	3.07±0.329	2.73±0.35	0.219
Lens thickness (mm)	4.27±0.311	4.26±0.325	4.49±0.389	0.006*
Corneal refractive power (D)	45.26±1.420	46.15±2.338	46.37±1.84	0.466
Mean myopic shift/year	−0.34±−0.2	−0.20±0.248	−0.54±0.45	0.592

The occurrence of myopia in our study cohort was 75%; high astigmatism was 31% and amblyopia 27.7%. Despite a 94% favorable structural outcome, functional outcome was favorable in only 79%. Lower gestational age in our study contributed to the development of larger refractive errors and lower visual acuity. At least three-fourth of the children in our study were myopic at the mean age of 7 years. Results of the ETROP reported 64.8%–69.9% of myopes at 6-year examination.[6] Our study population had higher rates of refractive errors in children treated for ROP than the earlier reported studies in the West.[2,11,19] Indian children belong to a diverse socioeconomic stratum with ROP developing in mature and higher birth weight babies.[13-16] There is evidence suggesting higher rates of myopia in Asian races in normal term children also.[20-22] Perhaps greater environmental factors contribute to the development of myopia in our children.

About 5.8% children in our study (four out of eight eyes) had a low vision despite a favorable structural outcome, without significant refractive error or strabismus. These unexplained visual losses could be a part of the subnormal visual acuity syndrome described in vision-screened population of children.[23] Could these be just an ametropic amblyopia occurring at low refractive errors? Considering the large life span of the child ahead, this is a significant number. An amblyopia as high as 27.7% along with anisometropia even in the presence of a good structural outcome comes as a surprise. There is a need for a longer follow-up, even in those children who have a favorable structural outcome after laser therapy.[24] Since a low refractive error might cause subnormal acuity, our threshold for prescription of glasses in these children should be lower than usual.

The exact refractive determinants of myopia in children with ROP is still a topic of debate.[2,7,11] Whether the influence on refractive errors in these children is caused by prematurity or ROP or both are poorly understood. On the other hand, laser treatment also influences emmetropization in these myopia prone premature eyes. There are numerous studies conducted on the refractive status and optical components in ROP babies and those who were lasered.[7,11,25-28] The proposed reasons for high myopia are a steep keratometry and a greater LT and a shallower ACD. The optical basis of myopia is a combination of these factors and may have little contribution from AL alone.[11] We do not have a study in the Indian population to determine the optical factors behind myopia in ROP. Our study results reveal a mean AL of 20.35 ± 1.65 mm despite myopia. We support the argument that ablation treatment over the whole circumference of the retina hampers ocular growth hence the decreased AL even in the presence of myopia.[29] There occurs a stunting of growth of the posterior segment of the eye, overcompensated by the anterior segment. Not only did we observe a shorter AL in a myopic eye but also lesser than the Western data in children treated for ROP (Mean AL ranged from 22.47 to 23.32 mm).[7,12,30] We observed a lenticular thickness of 4.33 ± 0.35 mm

and our study results indicate a lenticular nature of the myopia. Earlier studies observed an LT ranging from 3.46 to 3.95 mm.[7,30] We support the results of previously published literature in this regard.[7,11,30] Our study group had an ACD of 2.95 ± 0.47 and a mean keratometry value of 45.8 ± 1.89 D. We did see some steepening of the cornea (reported to vary between 44 and 45.24 D in other studies)[7,11] but this did not affect myopia in these eyes. A comparison of those with or without myopia reveals no significant difference in corneal curvature between the two. However, the lenticular thickness and AL were significantly more in high myopics as compared to those with no/low myopia [Table 3]. Hence, the AL may have more contribution to the development of "high myopia" in children treated for ROP. It is very difficult to isolate prematurity from ROP, hence very difficult to credit one optical component which determines the refractive error in this population of children lasered for ROP. To elucidate the role of laser therapy in contributing to myopia, the ideal control group would be ROP babies who were not lasered even in severe cases, which would imply denying such babies the standard of care and will not be feasible. Furthermore, environmental factors may trigger AL elongation and myopia in older children.[31,32] Hence, we observed a modest decrease in the ACD and an increase in AL in high myopes. The mean myopic shift/change in cylinder is similar to those reported in other term school going children with refractive errors.[33] Hence, it is safe to conclude, whatever refractive errors these children develop is largely dependent on the initial refractive error. Even those with high myopia have an average shift of − 0.5 D; which is expected in the normal development of myopia.[33] The anterior segment also gets arrested such as the posterior segment and the optical parameters of prematurity extend till adult age. After that, myopia progresses like any other myopic child with some contribution from the increasing AL or perhaps environmental triggers.

Astigmatism seen in these patients was not dependent on birth weight or gestational age. With the substitution of cryotherapy with laser, perhaps there is a tendency toward lesser astigmatism. Astigmatism seen was mostly with the rule, as seen in normal children also. In terms of outcome, severity of the disease and a lower gestational age at birth are conducive to poor visual acuity in these children. More the laser treated area, more the refractive error. While we cannot control the gestational age, the severity of disease can be controlled to some extent by stricter neonatal care and early treatment. Perhaps these refractive errors reinforce the need for better neonatal practices, less severe disease and timely referral to treat the disease as soon as possible.

The demerit of our study is its retrospective nature and lack of a comparative group. The longitudinal data at different time points was incomplete. Refractive error at a mean age of 7 years is not only affected by genetic factors or the disease but also environmental triggers which cannot be accounted for. Moreover, being a tertiary care center, there could always be a sampling bias in our study. Children with higher refractive errors and poor vision are more likely to be following up on a regular basis with the institute. This has the potential for skewing the results in favour of higher refractive errors and poorer visual acuity. Perhaps longer prospective and comparative trials would be better in this regard.

Conclusion

In summary, children with ROP may develop myopia and the mechanism of myopia may be multifactorial. We found myopia in our cohort to be mainly lenticular and greater AL contributing to its development. A severe disease with lower gestational age causes more myopic shift. Refractive state at 1 year error predicts the future development of myopia. There is a greater percentage of children who develop high astigmatism in the North Indian population. Different pattern of ROP and inherent genetic predisposition to myopia might be the influence on refractive errors in these children. There may be a need for a methodical follow-up in the children undergoing laser treatment for ROP to screen and correct even minor refractive errors.

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Conflicts of interest

There are no conflicts of interest.

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