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Refractive state and optical compositions of preterm children with and without retinopathy of prematurity in the first 6 years of life

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Abstract

This study aimed to investigate the refractive state and optical compositions of preterm children with and without mild retinopathy of prematurity (ROP) and explore the influence of prematurity and mild ROP on the development of refractive state and optical compositions.

Preterm children who received fundus screening were recruited, and divided into ROP group and non-ROP group. Term children matched in age were also recruited as controls. Several correspondence indicators were measured before and after ciliary muscle paralysis with 1% cyclopentanone.

A total of 250 eyes from 126 patients were included for analysis. The incidence of myopia was the highest in ROP group. The incidence of hyperopia was the highest in control group. The incidence of astigmatism was the highest in ROP group. The corneal astigmatism and mean astigmatism in ROP group and non-ROP group were significantly higher than in control group. Corneal refraction in ROP was markedly higher than in non-ROP group and control group; corneal curvature in ROP group increased significantly as compared with non-ROP group and control group ($P < .05$). The axial eye length in ROP group and non-ROP group reduced significantly as compared with control group ($P < .05$). Gestational age had negative relationships with corneal astigmatism ($P = .019$) and astigmatism ($P = .001$) and positive relationship with axial eye length ($P = .005$). Birth weight had negative relationships with corneal astigmatism ($P = .001$), astigmatism ($P < .001$), corneal refraction ($P = .001$), and corneal curvature ($P = .001$) and positive relationships with axial eye length ($P = .001$) and spherical equivalent refraction ($P = .039$). The incidence of myopia increased and that of hyperopia reduced in children over age. In children aged 3 to 4 years, the anterior chamber depth, lens thickness, vitreous thickness, and axial eye length significantly increased as compared with those aged 5 years ($P < .05$); the vitreous thickness and axial eye length in children aged 5 years increased significantly as compared with those aged 6 years ($P < .05$).

This study shows that preterm children with and without mild ROP are more likely to develop myopia and astigmatism, and low birth weight, prematurity, and ROP may simultaneously affect the development of optical compositions, leading to myopia and astigmatism.

Abbreviations: ROP = retinopathy of prematurity, SER = spherical equivalent refraction.

Keywords: low birth weight, optical composition, premature baby, refractive state, retinopathy of prematurity

1. Introduction

The survival rate of preterm babies and low birth weight infants increases progressively with the development of technology and perinatal medicine, but these children often develop eye problems in later life. The incidence of retinopathy of prematurity (ROP) tends to increase worldwide and has been a major cause of blindness and visual impairment in children.[1,2] Studies have confirmed that the incidences of myopia, astigmatism, strabismus, amblyopia, anisometropia increase in ROP children as compared with healthy children,[3–5] and myopia has been regarded as an important cause of blindness and visual impairment by World Health Organization. Increasing studies indicate that the incidence of myopia in preterm children with and without ROP is significantly higher than in full-term children.[6–8] For full-term babies, the eyes are in a hyperopia state at birth, but both eyes are in emmetropia or myopia state at birth for preterm babies. Some studies report that the incidence of myopia has negative relationships with birth weight and gestational age and has a positive relationship with the severity of ROP.[3] However, the pathogenesis of myopia in preterm babies is still unclear, and some studies report that the occurrence of myopia is related to the elevated corneal astigmatism, reduced anterior chamber depth, and increased refraction of lens.[9–11] To date, few studies have been conducted to investigate the optical compositions in preterm children with and without ROP, most studies focus on the refractive state of preterm infants and ROP children, and information about the refractive state in childhood is limited. In

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addition, some clinicians pay much attention to the ROP children receiving cryotherapy and photocoagulation and long-term follow-up is conducted in these children, but the long-term refractive state and visual development are still unclear in children with mild ROP who account for a majority of ROP children.

In our previous studies,[12,13] we investigated the refractive state and optical compositions in children (3–5 years old) with mild ROP, preterm children with low birth weight, and age-matched full-term children, and results showed that ROP children were more likely to develop myopia and astigmatism. In this study, similar examinations were performed in children aged 6 years and younger, aiming to explore the influence of ROP and prematurity on the refractive state and optical composition development and the changes in optical compositions.

2. Material and methods

2.1. General information

This study has been approved by the Ethics Committee of Affiliated Children's Hospital of Chongqing University. Preterm children who received fundus screening between January 2009 and February 2011 were recruited from the Department of Ophthalmology in the Affiliated Children's Hospital of Chongqing Medical University and divided into 2 groups according to the ROP. In addition, age-matched full-term children were recruited as controls. There were 56 eyes from 29 preterm children with ROP (stage 1–3 prethreshold) (ROP group), 104 eyes from 52 preterm children without ROP (non-ROP group), and 90 eyes from 45 healthy controls (control group). At 6 years old, the corneal refraction, corneal curvature, anterior chamber depth, lens thickness, vitreous thickness, and axial eye length were measured, and retinoscopy was performed after ciliary muscle paralysis. Moreover, the gestational age and birth weight were also recorded. The inclusion and exclusion criteria were as follows. A total of 132 children met the criteria, of whom 2 patients had incomplete information and 4 were lost to follow-up or refused to receive follow-up. Finally, 126 children were included in the analysis.

Inclusion criteria included gestational age was shorter than 37 weeks and birth weight was lower than 2500 g[14]; their parents or legal guardians agreed with examinations, children had good compliance, and informed consent was obtained before study; children had no central nervous system or circulatory system diseases (such as cerebral palsy and congenital heart disease); the refractive media had no turbidity and retinoscopy was feasible; and organic eye diseases except for ROP were not observed.

Exclusion criteria included gestational age was ≥37 weeks or birth weight was ≥2500 g; their parents or legal guardians were unavailable or refused to receive examinations; children had incomplete information due to poor compliance or inaccurate results due to cognition impairment; refractive media had turbidity, pupil enlargement was not observed, and there were other factors related to refractive difficulty; and children had a family history of high myopia.

2.2. Screening for ROP

The first examination was performed at 4 to 6 weeks after preterm birth or at corrected gestational age of 32 weeks. ROP was staged according to the International Classification of Retinopathy of Prematurity developed by The Committee for the Classification of Retinopathy of Prematurity in 1984[15]: examination was done once weekly for zone II stage 1 and 2 lesions without along with lesion and zone III stage 1 and 2 lesions; examination was done once every 2 to 3 days for pre-threshold lesions and the fundus was closely monitored; laser therapy or cryotherapy was performed within 72 hours for threshold lesions; surgery was done for staged 4 or 5 lesions; children were followed up once every 2 weeks if incomplete vascularization was observed at peripheral retina in the absence of ROP, until complete vascularization of the retina.

2.3. Eye examinations

At 6 years old, all the children received following eye examinations: corneal refraction, corneal curvature, anterior chamber depth, lens thickness, vitreous thickness, and axial eye length. In addition, retinoscopy was performed after ciliary muscle paralysis. Corneal refraction, corneal curvature, and corneal astigmatism were measured with an autorefractor (RK-8100; Topcon, Tokyo, Japan). Measurement was done thrice and a mean was calculated.[16] Anterior chamber depth, lens thickness, vitreous thickness, and eye length were measured with an eye ultrasonic instrument (KANGH CAS-2000, Kanghua Technology Co., LTD, Chonqqing, China). Measurement was done 8 times, and a mean was calculated.

2.3.1. Retinoscopy.

After administration with 1% cyclopentolate eye drop, the ciliary muscle paralysis was examined according to the pupillary light reflex. The absence of pupillary light reflex and the pupil diameter larger than 6 mm are suggestive of ciliary muscle paralysis (the pupil diameter might be not larger than 6 mm, but pupillary light reflex was absent). Then, retinoscopy was a bind-like ophthalmoscope (YZ24; 66 Vision Tech Co., Ltd., Suzhou, China).[17]

2.3.2. Data collection and processing.

Automatic optometry, eye ultrasonography, drug administration, retinoscopy, and data processing were performed by distinct investigators, and these investigators were blind to the study design. Refraction was expressed as spherical equivalent refraction (SER): SER = spherical refraction + 1/2 cylindrical refraction. The refraction distribution was expressed as mean refraction ($X \pm SD$). Hyperopia was defined as SER ≥+2.00 D; myopia was defined as SER ≤−0.50 D; astigmatism was defined as absolute cylindrical refraction ≥1.00 DC; high astigmatism was defined as absolute cylindrical refraction ≥3.00 DC.[18] Data of each eye were included for further analysis.

2.4. Statistical analysis

All the data were sorted and recorded in sheets, and statistical analysis was performed with SPSS version 20.0 (IBM, NY) The incidences of myopia, hyperopia, and astigmatism were compared with Chi-square test or Fisher exact test. Comparisons between 2 groups were further done with $\alpha = 0.05/3 = 0.0167$ if significant difference was observed among 3 groups.

Continuous variables (means) were compared with 1-way analysis of variance among 3 groups. A value of $P < .05$ was considered statistically significant. Least Significant Difference test was employed for comparisons between 2 groups if significant difference was observed among 3 groups.

The correlations of birth weight and gestational age with refractive state and optical compositions were evaluated with Pearson correlation coefficient. Independent sample t test was employed for the comparisons of refractive media in children of different age groups.

3. Results

Of 126 children, there were 58 boys and 68 girls with the mean age of 6.35±0.33 years. The mean gestational age was 34.42±4.530 weeks and the mean birth weight was 2221.40±758.25 g. In addition, 29 preterm children were diagnosed with ROP, including 16 boys and 13 girls; 52 preterm children had no ROP, including 24 boys and 28 girls; there were 45 full-term children, including 18 boys and 27 girls. Of 29 children with ROP, stage 1 ROP was found in 17, stage 2 ROP in 3, stage 3 ROP in 1, and prethreshold ROP in 8, and none had threshold lesions. Moreover, 27 children had ROP in both eyes and 2 had unilateral ROP (1 in right eye and 1 in left eye).

There was no significant difference in the gender among 3 groups ($X^2=6.853$, $P=.448$) (Table 1). The gestational age was the shortest and the birth weight was the lowest in ROP group, followed by non-ROP group and control group ($F=409.682$, $P<.001$; $F=457.483$, $P<.001$) (Table 1). Paired comparisons showed that the gestational age was significantly different between ROP group and non-ROP group ($F=22.093$, $P<.001$), between ROP group and control group ($F=721.492$, $P<.001$), and between non-ROP group and control group ($F=10.256$, $P=.009$) (Table 1). Significant difference was also noted in birth weight between ROP group and non-ROP group ($F=10.256$, $P=.009$), between ROP group and control group ($F=995.284$, $P<.001$), and between non-ROP group and control group ($F=702.54$, $P<.001$) (Table 1).

3.1. Incidences of myopia, hyperopia, and astigmatism

The incidence of myopia was the highest in ROP group (8/56, 14.29%), followed by non-ROP group (7/104, 6.73%) and control group (2/90, 2.22%), showing significant difference among them ($X^2=6.514$, $P<.05$). Further paired comparisons revealed that there was no marked difference between ROP group and non-ROP group ($P>.05$), but a significant difference was noted between ROP group and control group and between non-ROP group and control group ($P<.05$). The incidence of hyperopia was the highest in control group (31/90, 34.44%), followed by ROP group (18/56, 32.14%) and non-ROP group (32/104, 30.76%), showing no marked difference among 3 groups ($X^2=1.697$, $P=.537$). The incidence of astigmatism was the highest in ROP group (24/56, 42.85%), followed by non-ROP group (19/104, 18.27%) and control group (8/90, 8.89%), showing significant difference among 3 groups ($X^2=18.049$, $P<.05$). Further paired comparisons revealed significant difference in the incidence of astigmatism between ROP group and non-ROP group ($X^2=14.664$, $P<.05$) and between non-ROP group and control group ($X^2=5.794$, $P<.05$), but there was no marked difference between ROP group and non-ROP group ($X^2=3.231$, $P=.077$) (Figs. 1 and 2).

Table 1

Gender, gestational age, and birth weight in 3 groups.

	ROP group	Non-ROP group	Control group
Gender (M/F)	16/13	24/28	18/27
Gestational age*	29.61±1.12	31.67±1.41	39.26±0.71
Birth weight*	1452.24±65.96	1690.91±33.28	3309.43±52.96

ROP = retinopathy of prematurity.
* $P<.05$ among 3 groups (1-way analysis of variance; Least Significant Difference test).

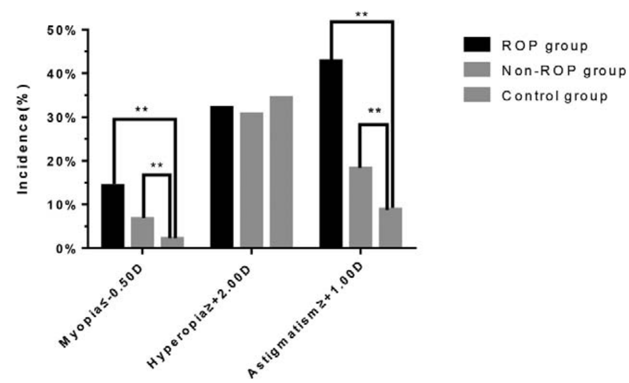

Figure 1. Different types of ametropia. X axis: definitions for hyperopia, myopia, and astigmatism. Incidences of hyperopia, myopia, and astigmatism were determined in ROP group, non-ROP group, and control group.

3.2. Refractive state and optical compositions

The corneal astigmatism was the highest in ROP group, followed by non-ROP group and control group, showing marked difference among them ($F=4.612$, $P=.011$; $F=6.287$, $P=.002$). Further analysis revealed significant difference in the corneal astigmatism between ROP group and control group and between ROP group and non-ROP group ($P<.05$), but there was no marked difference between control group and non-ROP group ($P>.05$). In addition, significant difference was not observed in the SER among 3 groups ($F=0.224$, $P=.800$). Significant differences were also noted in the corneal refraction ($F=7.845$, $P<.05$), corneal curvature ($F=7.385$, $P<.05$), and axial eye length ($F=5.635$, $P<.05$) among 3 groups. Further analysis indicated significant differences in the corneal refraction and corneal curvature between ROP group and non-ROP group and between ROP group and control group ($P<.05$), but marked differences were not observed between non-ROP group and control group ($P>.05$). The axial eye length was the longest in control group, followed by non-ROP group and ROP group, and a significant difference was observed between ROP group and control group and between control group and non-ROP group ($P<.05$), but there was no marked difference between ROP group and non-ROP group ($P>.05$). There were no significant differences in the lens thickness ($F=0.004$, $P=.996$), anterior chamber depth ($F=0.634$, $P=.532$), and vitreous thickness ($F=2.043$, $P=.133$) among 3 groups (Table 2).

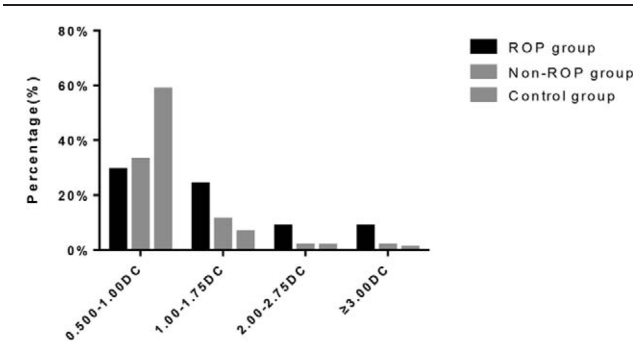

Figure 2. Distribution of astigmatism refractions.

Table 2

Refractive state and optical compositions in 3 groups.

		ROP group	Non-ROP group	Control group
Refractive state	Corneal astigmatism, D*	−1.48±0.93	−1.15±0.78	−1.04±0.45
	Astigmatism, D*	1.09±0.99	1.07±0.992	0.55±0.48
	SER, D	1.44±1.09	1.44±0.94	1.46±0.98
Optical compositions	Corneal refraction, D*	43.88±1.98	42.88±1.73	42.94±1.02
	Corneal curvature, mm*	7.87±0.36	7.66±0.30	7.65±0.31
	Anterior chamber depth, mm	3.05±0.25	3.00±0.22	3.03±0.24
	Lens thickness, mm	4.40±0.36	4.41±0.12	4.41±0.19
	Vitreous thickness, mm	15.11±0.82	14.86±0.63	15.10±0.58
	Axial eye length, mm*	22.35±0.98	22.36±0.69	22.57±0.58

ROP = retinopathy of prematurity, SER = spherical equivalent refraction.
* $P<.05$ among 3 groups.

3.3. Correlations of gestational age and birth weight with refractive state and optical compositions

Results of correlation analysis are summarized in Table 3. Gestational age had negative relationships with corneal astigmatism ($r=-0.204$, $P=.019$) and astigmatism ($r=-0.225$, $P=.006$) and a positive relationship with axial eye length ($r=0.258$, $P=.005$). Birth weight had negative relationships with corneal astigmatism ($r=-0.278$, $P=.001$), astigmatism ($r=-0.282$, $P<.001$), corneal refraction ($r=-0.252$, $P=.001$), lens thickness ($r=-0.246$, $P=.001$), and corneal curvature ($r=-0.245$, $P=.001$), and had positive relationships with axial eye length ($r=0.248$, $P=.001$) and SER ($r=0.156$, $P=.039$). Lens thickness, vitreous thickness, and anterior chamber depth had no relationships with gestational age and birth weight.

3.4. Optical compositions in children aged 3 to 4, 5, and 6 years

As summarized in Tables 4 to 6, the anterior chamber depth, lens thickness, vitreous thickness, and axial eye length in children aged 3 to 4 years increased significantly as compared with children aged 5 years ($P<.05$). The vitreous thickness and axial eye length in children aged 5 years increased markedly as compared with children aged 6 years, but there were no significant differences in anterior chamber depth and lens thickness ($P>.05$).

Table 3

Correlation analysis of gestational age and birth weight with refractive state and optical compositions.

		Gestational age	Birth weight
Refractive state	Corneal astigmatism, D	$r=-0.204$*	$r=-0.278$†
	Astigmatism, D	$r=-0.225$†	$r=-0.282$‡
	SER, D	$r=-0.042$	$r=0.156$*
Optical compositions	Mean corneal refraction, D	$r=-0.076$	$r=-0.252$†
	Mean corneal curvature, mm	$r=0.065$	$r=-0.245$†
	Anterior chamber depth, mm	$r=0.015$	$r=-0.019$
	Lens thickness, mm	$r=-0.028$	$r=-0.089$
	Vitreous thickness, mm	$r=0.043$	$r=0.117$
	Axial eye length, mm	$r=0.258$†	$r=0.248$†

SER = spherical equivalent refraction.
* $P<.05$.
† $P<.01$.
‡ $P<.001$.

4. Discussion

In 1940s and 1950, ROP was initially regarded as an important cause of blindness in high-income countries because of the wide and unlimited application of oxygen in very low birth weight babies and pre-term neonates with gestational age < 32 weeks. It was the first epidemic of ROP.[19] Thereafter, the restriction of oxygen application in neonates significantly reduces the increased incidence of ROP-related blindness in preterm neonates, but the mortality and risk for cerebral palsy increase. Thus, the oxygen supplement is a double-edged sword, which has been accepted for more years.[20] Since 1970s, the incidence of prematurity is at a high level in high-income countries, which is a major cause of ROP. Most of preterm neonates had the gestational age of <28 weeks and it was regarded the second epidemic of ROP.[1] Recent studies reveal that ROP has been an increasingly important, but an avoidable cause of blindness in China, Southeast Asia, South Asia, Latin America, and Eastern Europe.[21–25]

Studies have shown that the prematurity increases the risk for visual impairment in later life, which may be related to the focal complications after delivery before the visual maturation.[3] For example, the risks for ROP and nervous system complications are very high in preterm neonates, and even neonates with gestational age of 32 to 36 weeks also have an elevated risk for visual impairment in later life.[5] The shallow anterior chamber, elevated corneal curvature, and spherical lens make the preterm neonates be susceptible to congenital myopia. Even in the absence of ROP, the development of anterior segment of the axis oculi is impaired, which shortens the axial eye length and reduces the anterior chamber depth. These, together with the elevated lens thickness, increase the risk for myopia.[10,11]

Our results showed that the incidence of myopia was 14.29% in preterm children with ROP, 6.73% in preterm children without ROP, and 2.22% in full-term children, which were higher than that reported in children aged 3 to 5 years.[13] The incidence of myopia in ROP children was closed to that reported

Table 4

Optical compositions in ROP children of different age groups (x±S).

Age, y	Anterior chamber depth, mm	Lens thickness, mm	Vitreous thickness, mm	Axial eye length, mm
3–4	2.93±0.03	4.37±0.27	14.47±0.09	21.78±0.10
5	3.07±0.24	4.41±0.26	15.08±0.95	22.15±1.06
6	3.05±0.25	4.40±0.36	15.11±0.82	22.35±0.98

Table 5

Optical compositions in non-ROP children of different age groups (x±S).

Age, y	Anterior chamber depth, mm	Lens thickness, mm	Vitreous thickness, mm	Axial eye length, mm
3–4	2.99±0.02	4.36±0.26	14.51±0.06	21.86±0.07
5	3.01±0.21	4.41±0.22	14.74±0.67	22.16±0.75
6	3.00±0.22	4.41±0.12	14.86±0.63	22.36±0.69

by Robaei et al (15.0%),[5] but lower than that reported by Davitt et al (64.5%).[26] In the study of Davitt et al,[26] the birth weight was <1251 g and most neonates required treatments, but the mean birth weight was 2174.32±658.78 g in our study, which might be related to the difference in the results because very low birth weight is one of important risk factors of myopia. In addition, the incidence of myopia (58%) reported by Quinn et al[27] was also higher than that in the present study, which might be ascribed to the same reason.

Our results showed that the incidence of hyperopia was 32.14% in ROP children, which was significantly lower than that reported in children aged 3 to 5 years,[12,13] but closely to that reported by Quinn et al (35.3%)[27] and higher than that reported by Chen et al (23%).[9] This might be ascribed to the difference in the study population. In the study of Chen et al, they investigated children aged 7 to 9 years, and it is well known that the both eyes become emmetropic over age and thus the incidence of hyperopia reduces.

In our study, the incidence of astigmatism was 42.85% in ROP children, 18.27% in preterm children without ROP, and 8.89% in full-term children, showing marked difference among groups ($P<.05$) and it was negatively related to the gestational age and birth weight. The incidence of astigmatism in our study was lower than that reported by Davitt et al (52%),[17] which might be ascribed to the difference in birth weight. In the study of Davitt et al,[17] the birth weight was <1251 g, and astigmatism of ≥1.00 D and ≥2.00 D was observed in 50% and 25% of children at the age of 6 years. However, in the study of Robaei et al,[5] the incidence of astigmatism was 8.5% in children with birth weight of 1500 to 2449 g and 6.8% in those with gestational age of 32 to 36 weeks, but both factors were not simultaneously taken into account in the investigation of incidence of astigmatism. In our study, most children had the birth weight of <1500 g and gestational age of <32 weeks. Correlation analysis revealed that the lower the birth weight and the smaller the gestational age, the higher the astigmatism, which was consistent with the findings in children aged 3 to 5 years. This further confirms that small gestational age, low birth weight, and ROP may increase the risk for astigmatism.

Table 6

Optical compositions in full-term children of different age groups (x±S).

Age, y	Anterior chamber depth, mm	Lens thickness, mm	Vitreous thickness, mm	Axial eye length, mm
3–4	2.97±0.03	4.47±0.22	14.68±0.07	22.12±0.08
5	3.04±0.23	4.41±0.23	14.99±0.58	22.47±0.56
6	3.03±0.24	4.41±0.19	15.10±0.58	22.57±0.58

Studies have indicated that prematurity has a significant influence on the optical compositions and the development of refractive state, and the mechanism is very complex.[16] It has been reported that reduced anterior chamber depth, elevated corneal curvature, increased lens thickness, and increased refraction are all the contributing factors of ametropia in preterm children.[18,28] In preterm neonates, the development of eyes is slower than in full-term neonates, which reduces the axial eye length and increases the corneal curvature and lens refraction to assure the emmetropization. If this process is out of control, the risk for myopia increases. Our study indicated that preterm children with and without ROP had increased corneal curvature, reduced anterior chamber depth, increased lens thickness, and reduced axial eye length, which was consistent with the findings reported by Iwase et al.[16] In the study of Chen et al,[9] ROP children has steeper vertical corneal curvature ($P=.003$) and horizontal corneal curvature ($P=.031$) as compared with age-matched full-term children, which was similar to our findings.

As compared with children aged 3 to 5 years, some refractive compositions increased over age. The anterior chamber depth and lens thickness in children aged 5 years reduced significantly as compared with those aged 3 to 4 years, but there were no marked differences between children aged 5 years and those aged 6 years ($P>.05$). The vitreous thickness in children aged 5 years increased marked as compared with children aged 3 to 4 years ($P<.05$), but there was no significant difference between children aged 5 years and those aged 6 years in both ROP group and non-ROP group ($T=-0.117$, $P=.907$; $T=-1.330$, $P=.184$), and a significant difference was observed between them in control group ($T=-2.112$, $P=.035$). The axial eye length increased over age, but there was no significant difference ($P>.05$). Hyman et al[29] investigated 469 children aged 6 to 11 years, and 3-year follow-up showed that the axial eye length tended to increase over age. Axer-siegel et al[30] found that the axial eye length, anterior chamber depth, and vitreous thickness tended to increase over age in the infant stage of preterm children, but the lens thickness has no relationship with age. These findings were consistent with our results. In our future studies, we will further investigate the changes in refractive compositions over age.

There were still limitations in this study. More studies with large sample size are needed to investigate the influence of prematurity on the basis of corrected gestational age and birth weight. More elegant statistical analyses are required for the in-depth studies. In addition, in our study, children with threshold ROP who received surgical treatment were unavailable in our hospital, and more cases are needed to enrich our findings.

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