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Original Article

Refractive status and optical components of premature babies with or without retinopathy of prematurity at 3-4 years old

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Abstract: Purpose: To investigate the refractive status and optical components of premature babies with or without retinopathy of prematurity (ROP) at 3-4 years old, and to explore the influence of prematurity and ROP on the refractive status and optical components. Methods: Premature babies receiving fundus examination were recruited into ROP group and non-ROP group, with age-matched full-term babies as controls. Results: The incidence of myopia was the highest in ROP (3/59, 5.08%). The incidence of astigmatism was significantly different between ROP (37.29%, 22/59) and controls (17.86%, 15/84). The corneal refractive power in ROP and non-ROP was more potent compared with controls ($P<0.05$); corneal curvature was steeper ($P<0.05$); lens thickness was thinner ($P<0.05$); ocular axial length was shorter $P<0.05$). The gestational age was negatively related to corneal astigmatism and astigmatism, positively associated with vitreous thickness and axial length. The birth-weight was negatively associated with corneal astigmatism, astigmatism and corneal refractive power, positively related to corneal radius of curvature, vitreous thickness and ocular axial length. Conclusion: Premature babies with or without ROP are susceptible to myopia and astigmatism. ROP, prematurity and low birth-weight synergistically influence the development of refractive status and optical components, of which the prematurity and low birth-weight are more important.

Keywords: Prematurity, low birth-weight, retinopathy of prematurity, optical components, refractive status

Introduction

Multiple factors may influence the refractive status of children. Preschool children have less time of screen contact and thus less influenced by environmental factors. In these children, the refractive status is mainly affected by genetic, congenital factors and eye diseases in neonatal period such as Marfan's syndrome, congenital ptosis and retinopathy of prematurity (ROP). ROP refers to the proliferative retinopathy in premature babies and low birth-weight infants and accounts for 6-8% of causes of childhood blindness. Visual impairment and blindness due to ROP significantly influence the quality of life of premature babies [1]. ROP has been regarded a major cause of blindness in children of high and middle-income countries, and has been paid increasing attention to in developing countries [2].

Studies have been conducted to investigate the refractive status and optical components in premature babies and ROP babies in some countries including USA [3], UK [4], Japan [5] and Korea [6]. The findings vary due to differences in the methodology, live environment, socio-economic, health care and race. In China mainland and Taiwan [7, 8], similar studies have been conducted in some areas (such as Guangdong [9], Shenzhen [10], Zhejiang [11] and Jiangsu [12]). However, these are economically developed area and may not reflect the status of China. When compared with Guangdong and Shenzhen, a majority of cities in Western China have relatively underdeveloped, and the refractive status and optical components are less investigated in these underdeveloped areas.

The age of participants varied among previously reported studies which focused on infants

[9-11] or school-age children [8, 12], and few studies have been conducted in pre-school children [7]. In addition, a majority of participants in previous studies recruited subjects with threshold ROP, and few studies focused on the refractive status and optical components of subjects with pre-threshold ROP (or mild ROP [11]) although they have a larger proportion among subjects with ROP [9, 13]. Whether mild ROP and prematurity affect the development of refractive status and optical components of pre-school children and whether this influence is caused by mild ROP, prematurity or both are still poorly understood. The present study aimed to evaluate the refractive status and optical components of premature babies with and without ROP at 3-4 years old, and further to explore the influence of prematurity and ROP on the refractive status and optical status.

Materials and methods

General information

From January 2009 to February 2011, premature babies receiving fundus examination were recruited from the Children's Hospital of Chongqing Medical University, and full-term babies matched in age were also enrolled as controls. Premature babies were divided into ROP group and non-ROP group according to the findings from fundus examination. In ROP group, there were 59 eyes of 31 subjects with pre-threshold or lower stages; in non-ROP group, there were 118 eyes of 59 subjects without ROP; in control group, there were 84 eyes of 42 healthy babies. At 3-4 years after recruitment, the corneal refractive power, corneal curvature, anterior chamber depth, lens thickness, vitreous thickness, and ocular axial length were detected; retinoscopy was performed following cycloplegia. At the same time, the gestational age and birth-weight of these subjects were also recorded. Human subject research approval for the study protocol was obtained from WHO's Secretariat Committee on Research Involving Human Subjects. The study protocol was also approved by our hospital ethics committee. The protocol adhered to the provisions of the Declaration of Helsinki for research. On the basis of following exclusion criteria and inclusion criteria, 144 subjects were recruited, except 12 subjects had incomplete medical information and then were excluded. Thus, 132 subjects were included for final analysis.

Inclusion criteria: 1) Gestational age was <37 weeks and birth-weight was <2500 g [14]; 2) The parents or guardian agreed with examinations, babies cooperated with examinations and informed consent was obtained before study; 3) subjects had no diseases of central nervous system or circulatory system (such as cerebral palsy and congenital heart disease); 4) The refractive media had no turbidity and allowed retinoscopy; 5) There were no organic eye diseases except for ROP.

Exclusion criteria: 1) Gestational age was ≥37 weeks or birth-weight was ≥2500 g; 2) The parents or guardians of subjects were unavailable or refused the examination; 3) Subjects did not cooperate with examination causing incomplete information, or cognition dysfunction biased results; 4) There was any factor causing the turbidity of refractive media, the pupils failed to be enlarged or there were other factors resulting in refractive difficulty; 5) Subjects had a family history of high myopia.

Screening for ROP

First examination was performed at 4-6 weeks after birth or at the corrected gestational age of 32 weeks. According to the International Classification Criteria for Retinopathy of Prematurity (1984) [15], ROP was diagnosed: stage 1, 2 ROP in zone II without plus disease; stage 1, 2 ROP in zone III. Examination was done once weekly. For subjects with pre-threshold ROP, the ocular fudus was closely monitored, and examination was done once every 2-3 days; for subjects with threshold ROP, laser therapy or cryotherapy was performed within 72 h; subjects with 4-5 ROP received surgical intervention; Subjects without ROP and with incomplete vascularization of peripheral retina were followed up once every 2 weeks until retinal vascularization was present.

Ophthalmologic examination

A comprehensive ophthalmologic examination was done at 3-4 years after recruitment: detection of corneal refractive power, corneal curvature, anterior chamber depth, lens thickness, vitreous thickness, and ocular axial length as

Table 1. Characteristics of babies in 3 groups

	ROP group	Non-ROP group	Control group
Gender (M/F)	19/12	28/31	16/26
Gestational age*	29.71±0.33[a]	31.59±0.24[b]	39.17±0.29[c]
Birth-weight*	1444.36±63.98[a]	1645.68±46.38[b]	3313.43±54.96[c]

*Index means in the same line with different letters (a, b, c) were significantly different ($P<0.05$, ANOVA, least-significance-difference Method).

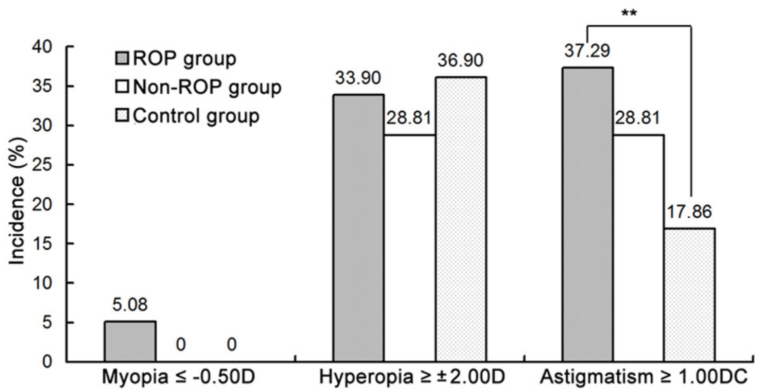

Figure 1. X-axis showed the criteria for myopia, hyperopia and astigmatism. The incidence of ametropia was calculated in ROP group, non-ROP group and control group. 0 means no myopia in non-ROP group and control group. $^{**}P<0.01$ among three groups (chi-square test).

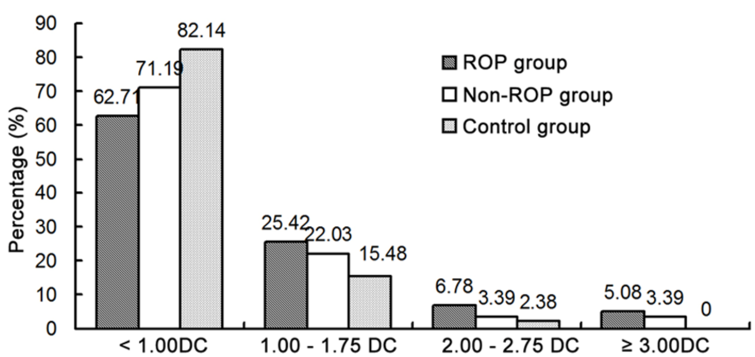

Figure 2. The distribution of astigmatism diopters in three groups. X-axis: cylinder diopter; 0: absence of high astigmatism in control group.

well as cycloplegic retinoscopy. Autorefractor (RK-8100; Topcon, Tokyo, Japan) was employed for the detection of corneal refractive power, corneal curvature and corneal astigmatism, which was performed three times, followed by calculation of means [16]. Anterior chamber depth (ACD), lens thickness (LT), vitreous thickness (VITR) and ocular axial length (AL) were detected with A-scan ultrasonograpy (KANGH CAS-2000, China). Before detection, surface anesthetic lidocaine was used for local anesthesia, and the probe was placed at the corneal center avoiding the oppression on the eye ball. Detection was done 8 times, followed by calculation of means [17]. Cycloplegic retinoscopy was performed: 1% cyclopentolate was used for cycloplegia. One drop was administered three times with the interval of 10 min. At 20 min after last administration of cyclopentolate, the degree of cyclopentolate was determined according to the pupillary light reflex. When the pupillary light reflex was present, another administration of cyclopentolate was done, and the degree of cyclopentolate was determined according to the pupillary light reflex and pupil size. Cycloplegia is defined as the pupil size larger than 6 mm and absence of pupillary light reflex. Streak retinoscope (YZ24; Six Vision Corp., Suzhou, China) was used for retinoscopy [18].

Data collection and processing

Autorefractor examination, A-scan ultrasonography, administration of drug drop, retinoscopy and data processing were performed by 5 investigators to reduce errors, and each investigator performed one examination. The participants, detector and data analyzer were blind to this study. Diopter was expressed as Spherical equivalent refraction (SER): SER= spherical refraction + 1/2 cylindrical refraction. The distribution of diopter was expressed as mean diopter X±SD. Hyperopia was defined when the SER was ≥+2.00D; myopia was defined when the SER was ≤-0.50D; astigmatism was defined when the absolute cylindrical refraction was ≥1.00DC. High astigmatism was defined when the absolute cylindrical refraction was ≥3.00DC. Data of each eye were input into a data sheet.

Statistical analysis

All the data were categorically recorded and listed, and statistical analysis was performed

Table 2. Comparisons of refractive status and optical status among 3 groups

		ROP group	Non-ROP group	Control group
Refractive status	Corneal astigmatism (D)*	-1.35±0.09[a]	-1.27±0.06[a]	-1.07±0.07[b]
	Astigmatism (D)*	0.89±0.09[a]	0.77±0.07[a]	0.55±0.08[b]
	Spherical equivalent fraction (D)	1.43±0.12	1.54±0.08	1.55±0.10
Optical component	Corneal refractive power (D)*	43.34±0.20[a,c]	43.87±0.14[a]	43.25±0.17[c]
	Corneal curvature (mm)*	7.78±0.04[a,c]	7.70±0.03[a]	7.81±0.03[c]
	Anterior chamber depth (mm)	2.93±0.03	2.99±0.02	2.97±0.03
	Lens thickness (mm)*	4.37±0.27[a]	4.36±026b[a]	4.47±0.22[b]
	Vitreous thickness (mm)	14.47±0.09	14.51±0.06	14.68±0.07
	Axial length (mm)*	21.78±0.10[a]	21.86±0.07[a]	22.12±0.08[b]

*Index means in the same line with different letters (a, b, c) were significantly different (*P*<0.05, ANOVA, least-significance-difference Method).

Table 3. Correlations analysis of gestational age and birth-weight with refractive status and optical components

		Gestational age	Birth-weight
Refraction	Corneal astigmatism (D)	r=-0.182**	r=-0.210**
	Astigmatism (D)	r=-0.207**	r=-0.216***
	Spherical equivalent fraction (D)	r=0.079	r=0.051
Optical components	Corneal refractive power (D)	r=-0.103	r=-0.226***
	Corneal curvature (mm)	r=0.104	r=0.225***
	Anterior chamber depth (mm)	r=0.075	r=0.060
	Lens thickness (mm)	r=0.113)	r=0.164**
	Vitreous thickness (mm)	r=0.138*	r=0.233***
	Axial length (mm)	r=0.181**	r=0.277***

*P<0.05 vs. refraction or optical components; **P<0.01 vs. refraction or optical components; ***P<0.001 vs. refraction or optical components.

with SPSS version 20.0. Incidences of myopia, hyperopia and astigmatism were compared with chi-square test, Fisher exact test was used when 20% of theoretical frequency was <5. Once significant difference was observed after analysis of variance, paired comparisons were performed three times, and α was 0.0167. The means of continuous variables were compared with analysis of variance among 3 groups, and a value of *P*<0.05 was considered statistically significant. When significant difference was observed after analysis of variance, LSD t test was performed. Pearson correlation coefficient was calculated to evaluate the correlations of birth-weight and gestational age with refractive status and optical components.

Results

Among the 132 subjects (64 males and 68 females), the mean age was 4.01±0.04 years. The mean gestational age was 33.56±4.33 W at birth, and the mean birth-weight was 2134.77±896.97 g. In addition, 31 subjects were included in ROP group (19 males and 12 females), there were 59 subjects in non-ROP group (28 males and 31 females), and 42 subjects were included in control group (16 males and 26 females). Of 31 subjects with ROP, 17 had stage 1 ROP, 4 had stage 2 ROP, 1 had stage 3 ROP, 9 had pre-threshold ROP and none had threshold ROP. Bilateral ROP was found in 28 babies and unilateral ROP was found in 3 babies (right eye in 1 and left eye in 2).

There was no significant difference in the gender among three groups (X^2=3.849, P=0.146) (**Table 1**). Of three groups, the gestational age was the smallest and the birth-weight was the lowest in ROP group, followed by non-ROP group and control group, and marked differences were observed in the gestational age and birth-weight among the three groups (F=291.411, P<0. 001; F=350.956, P<0.001) (**Table 1**). Further paired analysis showed significant differences in gestational age and birth-weight between any two groups (P<0.01) (**Table 1**).

Incidence of ametropia and astigmatism diopter among three groups

The incidence of myopia was 5.08% (3/59) in ROP group, but myopia was not found in other groups. The incidence of hyperopia was the highest in control group (31/84; 36.90%), followed by ROP group (20/59; 33.90%), and non-ROP group had the lowest incidence of hyperopia (34/118; 28.81%). There was no marked difference in the incidence of hyperopia (X^2=1.524, P=0.467). The incidence of astigmatism in ROP group (22/59; 37.29%) was higher than that in non-ROP group (34/118; 28.81%) and control group (15/84; 17.86%), and significant difference was observed between ROP group and control group (X^2=6.823, P=0.009). The incidence of astigmatism was comparable between ROP group and non-ROP group (X^2=1.306, P=0.253) as well as between non-ROP group and control group (X^2=3.206, P=0.073) (**Figure 1**).

Among three groups, mild astigmatism was found in a majority of subjects, and few subjects were diagnosed with high astigmatism. Among subjects with astigmatism of <1.00DC, 80% was in the control group, followed by non-ROP group and ROP group. Of subjects with astigmatism of ≥1.00DC, the number of subjects in ROP group was larger than that in non-ROP group and control group. High astigmatism (≥3.00DC) was mainly found in ROP group (5.08%) and non-ROP group (3.39%), showing no significant difference (X^2=0.349, P=0.555). High astigmatism was not found in control group (**Figure 2**).

Refractive status and optical components

Table 2 showed the results after comparisons of refractive status and optical components among the three groups. In respect of refractive status, ROP group had the highest corneal astigmatism and astigmatism diopter, followed by non-ROP group, and control group had the lowest corneal astigmatism and astigmatism diopter (F=3.474, P=0.032; F=4.199, P=0.016). Significant differences were observed in the corneal astigmatism and astigmatism diopter between ROP group and control group (P<0.05), not between ROP group and non-ROP group as well as between non-ROP group and control group (P>0.05) (**Table 2**). The spherical equivalent refraction was comparable among three groups (F=0.325, P=0.723). In respect of optical components, marked differences were observed in the corneal refractive power (F=4.339, P=0.014), corneal curvature (F=3.916, P=0.021), Lens thickness (F=4.647, P=0.01) and axial length (F=4.523, P=0.012) among three groups. There were no significant differences in the anterior chamber depth (F=1.51, P=0.223) and vitreous thickness (F=2.261, P=0.106) among three groups. Further paired comparisons showed the lens thickness and axial length in control group were significantly different from those in ROP group and non-ROP group (P<0.05), and significant differences in the corneal refractive power and corneal curvature were observed only between non-ROP group and control group (P<0.05). There were no significant differences in the refractive status, optical components and axial length between ROP group and non-ROP group (P>0.05) (**Table 2**).

Table 3 shows the correlations analysis of gestational age and birth-weight with refractive status and optical components. Gestational age was negatively related to corneal astigmatism (r=-0.182, P=0.003) and astigmatism (r=-0.207, P=0.001), but positively associated with vitreous thickness (r=0.138, P=0.026) and axial length (r=0.181, P=0.003). The birth-weight was negatively related to corneal astigmatism (r=-0.210, P=0.001), astigmatism (r=-0.216, P<0.001) and corneal refractive power (r=-0.226, P<0.001), but positively associated with corneal curvature (r=0.225, P<0.001), vitreous thickness (r=0.233, P<0.001) and axial length (r=0.277, P<0.001). Spherical equivalent fraction (r=0.079, P=0.206; r=0.051, P=0.416) and Anterior chamber depth (r=0.075, P=0.226; r=0.060, P=0.337) were not related to the gestational age and birth-weight.

Discussion

The late embryonic phase and early phase after birth are crucial for the development of eyes, especially the refractive media. In premature babies, especially ROP babies, the eye development and subsequent emmetropization may be influenced due to prematurity [19, 20]. A large amount of evidence shows full-term babies are generally in a hyperopia status, but premature babies, regardless ROP, have high risks for myopia [2, 3], astigmatism [2, 21], anisometropia [22] and strabismus [23]. Our study investigated the refractive status and optical components in premature babies with ROP at pre-threshold or lower stages at 3-4 years old. Our results showed ROP babies had a higher risk for ametropia and the ametropia in ROP babies was higher. In the present study, myopia was found in only ROP group, and the incidence and severity of astigmatism were the highest in ROP group (**Figure 1**). The axial length was the shortest in ROP group (**Table 2**).

The occurrence of myopia is mainly influenced by genetic and environmental factors, and the region, race, age and gender may also contributing factors of myopia. In the present study, the incidence of myopia was 5.08% among eyes with ROP, and premature babies without ROP and full-term babies had no myopia. This incidence of myopia in ROP affected eyes was lower than that reported by Fledelius et al (25%) [20] and Quinn et al (35%) [24]. In addition, in premature babies, the incidence of myopia in eyes without ROP was lower than that reported by Fledelius et al (5%) [20] and Quinn et al (10%) [24]. This may be explained as follows: the participants in our study were preschool children aged 3-4 years who were younger than those in other studies (7-10 years old in the study of Fledelius et al; 5.5 years old in the study of Quinn et al), and the myopia deteriorates over age. Learning strength and doing homework at a short distance are also important causes of myopia, which has been confirmed in the study of Yin et al [18]. In our study, babies aged 3-4 years had less time of screen contact and doing homework at a short distance. In the present study, premature babies with birth-weight of <2500 g were recruited, which was higher than that in previous studies (≤1251 g [3], ≤1500 g [8] and <1701 g [7]). Yang et al [9] also found that low birth-weight increased the incidence of myopia. Thus, the relatively low incidence of myopia might be also ascribed to a relatively high birth-weight in the present study. In our study, myopia was found in only ROP group, suggesting that ROP, small gestational age and low birth-weight may increase the risk for myopia.

In our study, the incidence of astigmatism was 37.29% in ROP affected eyes, 28.81% in premature babies and 17.86% in full term babies. High astigmatism was only found in ROP group (5.08%) and non-ROP group (3.39%). The incidence of astigmatism was 37.29% in ROP affected eyes, which was consistent with that reported by Davitt et al (42%) [21]. The incidence of high astigmatism lower than previous reported (20%) might be ascribed to more severe ROP and laser therapy perfirmed in previous studies. In our study, babies with ROP at threshold or lower stage were recruited and laser therapy and surgery were not performed in these babies. Laser therapy or surgery may cause formation of retinal scars which might cause high astigmatism [21]. In the present study, the incidence of astigmatism was 28.81% in the eyes of premature babies, which was consistent with previously reported [2]. The mean astigmatism diopter was 0.89D in ROP group, which was consistent with previously reported by Xia et al (0.75D) [11] and Chen et al (1.00D) [25]. Correlation analysis showed low birth-weight and small gestational age were related to high astigmatism diopter. Thus, we speculate that low birth-weight and ROP may increase the risk for astigmatism. Our results also revealed that the incidence of astigmatism was significantly different between ROP group and control group, but there was no marked difference between non-ROP group and ROP group/control group. This suggests that prematurity and mild ROP synergistically increase the incidence of astigmatism.

Refractive status is as a result of multiple optical components, and corneal curvature, anterior chamber depth, lens thickness, vitreous thickness and axial length play important roles in the emmetropization of eyes, of which the corneal curvature, refractive power of the lens and axial length contribute more to the emmetropization of eyes. Our results showed the corneal refractive power in ROP group and non-ROP group were more potent than that in control group, and the corneal curvature was steeper in former two groups, which were consistent with previously reported by Cook et al [1] and Wang et al [17]. In ROP group and non-ROP group, the lens thickness was thinner than that in control group, which was less investigated in studies. Further studies with large sample size are required to confirm our findings. The ocular axial length in ROP group and non-ROP group was shorter than that in full-term babies. Cook et al [13] reported that, early infancy stage, the axial length in premature babies was shorter than that in full-term babies. Ecsedy et al [26] found the ocular axial length in premature children with and without ROP at

7-14 years old was shorter than that in full-term children. Their findings indirectly supported our results. No significant differences were observed in the refractive status, optical components and axial length between ROP group and non-ROP group, suggesting that prematurity and low birth-weight are important factors affecting the development of refractive components, and mild ROP has a minor role.

Our results showed the smaller the gestational age, the higher the corneal astigmatism and astigmatism diopter were, the thinner the vitreous thickness was and the shorter the ocular axial length was; the lower the birth-weight, the higher the corneal astigmatism, astigmatism diopter and corneal refractive power were, the steeper the corneal curvature was, the thinner the vitreous thickness was and the shorter the ocular axial length was. Zhou et al [12] and Ozdemir et al [27] reported that the vitreous thickness and ocular axial length reduced with the reductions in gestational age and birth-weight. Friling et al [28] reported that the corneal refractive power was reversely related to the gestational age and birth-weight in neonates. Above findings were consistent with our results, and also supported our conclusion that ROP, prematurity and low birth-weight synergistically affect the development of refractive status and optical components, of which prematurity and low birth-weight contribute more.

There were limitations in the present study. It is better to use corrected gestational age in future studies. In next study, we will recruit more participants and control the differences in gestational age and birth-weight between ROP group and non-ROP group, which may exclude the influence of gestational age and birth-weight on the development of refractive status and optical components. Information on the ROP babies receiving laser therapy was not included in the present study, and will be evaluated in our future studies. In addition, the refractive status and optical components were investigated in only babies at 3-4 years, and whether the influence of ROP and prematurity on the eye development still persists over age is required to be further studied. In our future studies, we will continue to follow up babies in the present study.

Conclusions

Premature babies with or without ROP are susceptible to myopia and astigmatism. ROP, prematurity and low birth-weight synergistically influence the development of refractive status and optical components, of which the prematurity and low birth-weight are more important.

Disclosure of conflict of interest

None.

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