Foveal morphology of retinal layers in 4 to 6-year-old children with history of retinopathy of prematurity: J-CREST study

Tomo Nishi (tomon@naramed-u.ac.jp)
Nara Medical University
Tetsuo Ueda
Nara Medical University
Yuutaro Mizusawa
Nara Medical University
Kayo Shinomiya
Tokushima University
Yoshinori Mitamura
Tokushima University
Naoki Kimura
Hyogo College of Medicine
Fumi Gomi
Hyogo College of Medicine
Akiko Miki
Kobe University
Makoto Nakamura
Kobe University
Takamasa Kinoshita
Sapporo City General Hospital
Shumpei Obata
Shiga University of Medical Science
Masahito Ohji
Shiga University of Medical Science
Takuya Tsuji
Kurume University
Shigeo Yoshida
Kurume University
Nahoko Ogata
Nara Medical University

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Abstract

The most effective treatment for retinopathy of prematurity (ROP) is considered as the laser therapy. We compared the foveal morphology of the retina in eyes with a history of ROP with that of full-term children. This was a cross-sectional comparative study. Seventy-eight patients with a history of ROP, aged 4–6 years, were included. Among them, 45 underwent laser treatment for ROP. The clinical findings and retinal morphology in these patients were compared with that of 33 patients who had spontaneous regression of ROP and 30 age-matched full-term controls.

All patients with ROP had 20/40 or better best-corrected visual acuity (BCVA). The foveal thickness was significantly thicker and foveal depression was significantly shallower in laser-treated ROP eyes than in regressed ROP eyes and controls. The outer nuclear layer was significantly thicker, and the inner segment (IS) of the photoreceptors and the inner retinal layer (IRL) were significantly longer in the laser-treated ROP eyes than that in the control eyes. In ROP patients and controls, BCVA was associated with the foveal depression, foveal depression was associated with the gestational age and IS thickness was associated with ROP stage. Our results suggest that prematurity and laser treatment affect the foveal morphology and BCVA.

Introduction

Retinopathy of prematurity (ROP), which requires treatment, has increased with the development of perinatal care.[1] ROP has a higher incidence of myopia, amblyopia, retinal detachment, strabismus, cataracts, glaucoma, and macular folds.[1–5] Angiogenesis in the retina begins from the posterior pole at 24–28 weeks of gestational age, and the peripheral retina is finally vascularized at 40 weeks.[6] Thus, retinal development, including the migration and redistribution of photoreceptor cells, occurs *ex utero* in premature infants.[7]

Spectral-domain optical coherence tomography (SD-OCT) studies have shown several microstructural abnormalities in the eyes of premature infants, such as retention of the inner retinal layers (IRL) at the fovea and an absence of foveal depression in individuals aged 2–18 years with a history of premature birth.[8–12]

Laser therapy is considered the most effective treatment for ROP.[2,4] However, laser therapy destroys the peripheral retina and slows the abnormal growth of peripheral blood vessels.[2] There is no consensus regarding the effect of laser treatment on retinal immaturity, and the signs of immaturity could be a predictor of visual function.

Therefore, this study aimed to determine whether laser photocoagulation affects retinal maturation. To accomplish this, we analyzed the foveal morphology in children treated with laser photocoagulation for ROP. The findings in these children were compared to that of children whose ROP spontaneously regressed and age-matched full-term children.

Results

Seventy-eight children with a history of ROP were divided into two groups: the laser-treated ROP group and the spontaneously regressed ROP group. The laser-treated ROP group consisted of 45 patients, including 22 boys and 23 girls, and the mean age was 5.0 ± 0.8 years (mean ± standard deviation). The spontaneously regressed ROP group consisted of 33 patients (18 boys and 15 girls) with a mean age of 4.9 ± 0.8 years. The control group consisted of 30 children (12 boys and 18 girls) with a mean age of 5.0 ± 1.4 years (Table 1).

Table 1
Demographics of patients and controls

	Treated ROP (n = 45)	Regressed ROP (n = 33)	Control (n = 30)	P value[1] t-ROP vs r-ROP vs control	P value[2] t-ROP vs r- ROP	P value[2] t-ROP vs control	P value[2] r-ROP vs control
Gestational Age [week]	26.0 (2.3)	28.8 (3.3)	39.0 (1.9)	0.0001	0.0001	0.0001	0.0001
Birth Weight [g]	841.7 (274.5)	1094.3 (472.2)	2988.7 (462.1)	0.0001	0.0001	0.0001	0.0001
Sex [Boy / Girl]	22 / 23	18 / 15	12 / 18	0.926			
Assessment Age [years]	5.0 (0.8)	4.9 (0.8)	5.0 (1.4)	0.812			
Visual Acuity [logMAR]	0.03 (0.12)	0.06 (0.18)	-0.04 (0.05)	0.009	0.57	0.063	0.008
Spherical Equivalent [D]	-1.42 (3.00)	+ 1.00 (1.75)	+ 0.73 (1.41)	0.090			
Axial Length [mm]	21.8 (1.4)	21.4 (0.6)	22.2 (0.9)	0.006	0.219	0.179	0.004
ROP Stage	2.8 (0.5)	1.2 (1.1)		0.0001			
Data was expressed as mean (standard deviation).							
P value : 1 ANOVA 2 Tukey							
t-ROP: treated ROP, r-ROP: regressed ROP							

The age and sex distributions were not significantly different between the ROP patients and the control group (ANOVA).

The gestational age and birth weight were significantly lower in the laser-treated ROP group than that in the spontaneously regressed ROP and control groups ($P = 0.0001$, ANOVA).

The mean better best-corrected visual acuity (BCVA) at the initial examination was 0.03 ± 0.12 logMAR units in the laser-treated group, 0.06 ± 0.18 logMAR units in the regressed ROP group, and − 0.04 ± 0.05 logMAR units in the control group. The BCVA was significantly better in the control group ($P = 0.009$, ANOVA). All patients had BCVA of 20/40 or better.

The mean refractive error was − 1.42 ± 3.00 D in the laser-treated eyes, + 1.00 ± 1.75 D in the regressed eyes, and + 0.73 ± 1.41 D in the control eyes ($P = 0.090$, ANOVA). The mean axial length was 21.8 ± 1.4 mm in the treated eyes, 21.4 ± 0.6 mm in the regressed eyes, and 22.2 ± 0.9 mm in the control eyes ($P = 0.006$, ANOVA; Table 1).

Foveal thickness

The mean foveal thickness was 263.2 ± 26.2 μm in the laser-treated eyes, 241.1 ± 22.9 μm in the spontaneously regressed eyes, and 214.4 ± 13.4 μm in the control eyes ($P = 0.0001$, ANOVA; Table 2). The fovea was significantly thicker in the laser-treated eyes compared with the regressed and control eyes. The inter-observer reproducibility was excellent (intraclass correlation coefficients = 0.91).

Table 2
OCT findings of patients and controls

	Treated ROP (n = 45)	Regressed ROP (n = 33)	Control (n = 30)	P value[1] t-ROP vs r-ROP vs control	P value[2] t-ROP vs r- ROP	P value[2] t-ROP vs control	P value[2] r-ROP vs control
Foveal Thickness [μm]	263.2 (26.2)	241.1 (22.9)	214.4 (13.4)	0.0001	0.0001	0.0001	0.0001
Foveal Depression [μm]	58.2 (32.8)	75.3 (34.7)	124.5 (17.1)	0.0001	0.001	0.0001	0.0001
ONL Thickness [μm]	121.2 (11.7)	110.5 (20.0)	84.3 (12.4)	0.0001	0.0001	0.0001	0.0001
IS Thickness [μm]	46.1 (5.6)	43.2 (5.6)	38.5 (8.8)	0.001	0.91	0.0001	0.0001
OS Thickness [μm]	41.6 (4.0)	40.9 (5.0)	43.9 (3.2)	0.13			
IRL Thickness [μm]	9.5 (10.5)	3.7 (11.2)	0 (0)	0.0001	0.247	0.0001	0.019
				P value[3]			
Detection Rates of Inner Retinal Layer [%]	51.0	12.0	0	0.0001			
Data was expressed as mean (standard deviation).							
P value : 1 ANOVA 2 Tukey 3χ^2-test							
t-ROP: treated ROP, r-ROP: regressed ROP							

The mean foveal depression was 58.2 ± 32.8 μm in the treated eyes, 75.3 ± 34.7 μm in the regressed eyes, and 124.5 ± 17.1 μm in the control eyes. The foveal depression was significantly shallower in the laser-treated eyes than that in the regressed and control eyes (P = 0.0001, ANOVA; Table 2). The mean thickness of the outer nuclear layer (ONL) was significantly longer in the treated eyes than that in the regressed eyes and control eyes (P = 0.0001, ANOVA; Table 2). The length of the inner segment (IS) was significantly longer in the treated and regressed ROP eyes than that in the control eyes (P = 0.0001, ANOVA; Table 2). IRL was significantly longer in the laser-treated eyes than that in the regressed eyes and control eyes (P = 0.0001, ANOVA; Table 2). IRL was detected in 51.0% of the treated eyes and 12.0% of the regressed eyes; thus, IRL was significantly preserved in the laser-treated eyes, whereas it was not detected in the control eyes (*P* = 0.0001, χ^2-test; Table 2)

In the univariate analysis, BCVA was significantly associated with the gestational age, birth weight, refractive error, foveal depression and IS thickness in ROP treated eyes (Pearson’s coefficient; Table 3). In the regressed and control eyes, BCVA was not associated with the foveal morphology(Pearson’s coefficient; Table 3). In the multiple linear regression analysis of ROP and controls, better BCVA was significantly associated with the deeper foveal depression (*P* = 0.032; Table 4). In the multiple linear regression analysis of ROP and controls, deeper foveal depression was significantly associated with the mature gestational age (*P* = 0.024; Table 5). In the multiple linear regression analysis of ROP and controls, longer IS was significantly associated with the progressing ROP stage (*P* = 0.001; Table 6).

Table 3
The clinical elements affected on BCVA

	Treated ROP (n = 45)		**Regressed ROP (n = 33)**		**Control (n = 30)**	
	r	**P value**	**r**	**P value**	**r**	**P value**
Gestational Age (week)	**-0.364**	**0.015**	**-0.086**	**0.634**	**0.032**	**0.946**
Birth Weight (g)	**-0.307**	**0.043**	**-0.143**	**0.426**	**0.018**	**0.963**
Spherical Equivalent (D)	**-0.353**	**0.019**	**-0.452**	**0.008**	**0.266**	**0.155**
Axial Length (mm)	**0.108**	**0.517**	**0.231**	**0.196**	**0.01**	**0.958**
Foveal Thickness (μm)	**-0.118**	**0.447**	**-0.027**	**0.881**	**-0.158**	**0.404**
Foveal Depression (μm)	**-0.349**	**0.02**	**-0.214**	**0.231**	**-0.04**	**0.832**
ONL Thickness (μm)	**-0.002**	**0.992**	**0.225**	**0.207**	**-0.01**	**0.958**
IS Thickness (μm)	**-0.351**	**0.02**	**0.068**	**0.739**	**-0.081**	**0.699**
OS Thickness (μm)	**0.055**	**0.725**	**0.004**	**0.985**	**-0.242**	**0.197**
IRL Thickness(μm)	**0.057**	**0.714**	**0.013**	**0.942**		
ROP Stage	**0.075**	**0.63**	**0.088**	**0.628**		
Frequency of Laser Treatment	**0.079**	**0.171**				
Univariate linear regression analysis was performed.						

Table 4
Multiple linear regression analysis between visual acuity and independent variables

Independent variable	Visual Acuity (logMAR)	
	Standardized β	P value
Gestational age (week)	0.170	0.886
Birth weight (g)	-0.310	0.270
Foveal depression (μm)	-0.274	0.032
IS thickness (μm)	-0.173	0.195
ROP stage	-0.089	0.585
Laser treatment	0.066	0.580

Table 5
Multiple linear regression analysis between foveal depression and independent variables

Independent variable	Foveal depression (μm)	
	Standardized β	P value
Gestational age (week)	0.579	0.024
Birth weight (g)	-0.198	0.428
Axial length (mm)	-0.120	0.241
ROP stage	0.025	0.830
Laser treatment	-0.246	0.078

Table 6
Multiple linear regression analysis between IS thickness and independent variables

Independent variable	IS thickness (μm)	
	Standardized β	**P value**
Gestational age (week)	**0.119**	**0.627**
Birth weight (g)	**-0.34**	**0.164**
Axial length (mm)	**0.024**	**0.808**
ROP stage	**0.450**	**0.001**
Laser treatment	**0.178**	**0.116**

Representative ROP patient

Case 1

A 6-year-old boy was born at 25 weeks gestation and weighed 690 g at birth. He was classified with Zone 1 and stage 3 ROP with plus disease. The patient was treated with laser photocoagulation at 33-weeks-of-age. His BCVA was 20/40 Snellen equivalent in both eyes. The foveal depression was shallow at 22.5 μm in the OCT images, and the IRL of the fovea was preserved (Fig. 1A). The fovea was 239 μm thick. ONL was 133 μm, IS was 50 μm, Outer segment (OS) was 40 μm, and IRL was 33μm.

Case 2

A 4-year-old girl was born at 24 weeks gestation and weighed 640 g at birth. She was classified as Zone 3 stage 3 ROP without plus disease. ROP spontaneously regressed after 44 weeks in this case. Her BCVA was 20/25 Snellen equivalent in both eyes. The foveal depression measured 108.5 μm in the OCT images (Fig. 1B). IRL of the fovea was not detected and the foveal thickness was 218 μm. ONL was 92 μm, IS was 44 μm, OS was 43 μm, and IRL was not detected.

The foveal depression was deeper, IRL was shorter, and the visual acuity was better in the second case than that in the first treated case.

Discussion

We found that the patients with a history of ROP demonstrated macular morphological differences compared with full-term control children, that is, retention of IRL, shallower foveal depression, and longer ONL and IS. These findings indicate that there is an alteration in the retinal developmental process in eyes with ROP.

OCT findings

We observed a thicker ONL and resistance of IRL in children with ROP, which is in agreement with the results of previous reports.[9,13,14] Preterm birth between 24 and 28 weeks of gestation has been proposed as a critical period associated with a failure of normal migration of IRL away from the fovea, resulting in increased foveal thickness and resistance of IRL.[13,14] The migration of IRL appears to be independent of the outer retinal development, as previously suggested.[15] This disparity in maturation might be associated with the vascular supply differing between the inner and outer retina. The vasculature of the outer retina develops during the late stage of gestation.[16] IRL matures completely at the time of full-term birth; however, the maturity of the outer retina is not attained until a few years after birth.[13,14] The maturation of the outer retina includes the development of the IS and OS layers, which occurs after birth and continues up to 5 years of age.[7,17] These processes are disrupted by preterm birth and ROP. Thicker ONL and longer IS in children with ROP may be due to a delay in foveal maturation.[18]

Visual acuity

BCVA of the treated and regressed ROP patients was worse than that of the control children, although all ROP patients had 20/40 or better BCVA. In previous reports, some studies found that a thicker fovea resulted in poorer visual acuity in childhood.[10,19] Other study found no relationship between foveal thickness and visual acuity.[20] There is no consensus regarding the relationship between visual acuity and infant prematurity. In our study, BCVA of the treated ROP patients was significantly associated with early preterm birth, light birth weight, severe myopia, longer IS, and shallow foveal depression. Early preterm birth and light birth weight are signs of infant prematurity. Severe myopia in patients with ROP is affected by laser treatment.[10,19] Shallow foveal depression and longer IS in patients with ROP were signs of immaturity of the foveal development.[18] In our study, longer IS was significantly associated with the progressing ROP stage. Thus, BCVA is related to infant prematurity, foveal prematurity, and laser treatment.

The laser treatment of ROP

IS in the eyes of patients with ROP was longer than that in the control eyes; however, the IS length was not affected by the laser treatment. Premature neonates had a thin photoreceptor layer at the fovea on the SD-OCT images.[7] These studies demonstrated the presence of significant foveal cone specialization in the absence of a foveal pit.[21] The migration of the cells in IRL was independent of the photoreceptor development in the outer retinal layer.[15] The results of a recent study showed that maturation of the outer retinal layer and photoreceptors is delayed in laser-treated ROP eyes.[22] Vogel et al. reported that infants treated with IVB for ROP had more rapid outer retinal thickening at the fovea, while those treated with laser therapy showed delayed development of the ellipsoid zone at the fovea.[22] However, the structure-function correlations in these regions remain poorly understood. We studied children aged 4–6 years when the retina is still developing.[16,23] In these ages, foveal development can last, and the outer retina of patients with ROP is still developing.[23] Our results suggest that infant prematurity and laser treatment affect foveal morphology.

Limitations

This study had some limitations. The number of patients with ROP and controls was small. In addition, all participants were Japanese. We manually measured the retinal layers because of segmentation errors when the automated software was used.[24] The retinal thickness was measured using Spectralis OCT and Cirrus OCT. The differences between the two SD-OCT systems were due to the differences in their built-in software algorithms[25], and we measured the retinal thickness using ImageJ software.

Conclusion

In conclusion, the morphology of the fovea in the eyes of children with laser-treated ROP was significantly different from that of eyes with spontaneously regressed ROP and control eyes. In ROP patients and controls, BCVA was associated with the foveal depression, foveal depression was associated with the gestational age and IS thickness was associated with ROP stage. Our results suggest that infant prematurity and laser treatment affect foveal morphology and visual acuity.

Methods

This was a multicenter retrospective study of patients with a history of ROP who were diagnosed and followed up at the Nara Medical University Hospital, Tokushima University Hospital, Hyogo Medical University Hospital, Kobe University Hospital, Sapporo City General Hospital, Shiga Medical University Hospital, and Kurume University Hospital between April 2012 and December 2019.

The protocol for this study conformed to the tenets of the Declaration of Helsinki and was approved by the Internal Review Boards of the Nara Medical University, Tokushima University, Hyogo Medical University, Kobe University Hospital, Sapporo City General Hospital, Shiga Medical University Hospital, and Kurume University Hospital. For research involving human participants that are minors, informed consent was obtained from all their parents to perform the measurements and review their medical records.

All patients had a history of ROP and were followed up for 4–6 years. Patients who were capable of cooperating with the OCT examinations were included. Patients with organic eye diseases, history of intraocular surgery, cataracts, glaucoma, or any retinal disorders were excluded. Laser-treated ROP patients were treated at the pre-threshold ROP or threshold ROP stage.[26] Laser treatment was performed in the temporal quadrant in four eyes and all quadrants in the remaining eyes. The patients with spontaneously regressed ROP presented with stage 2 or less, and none of them had received any treatment for ROP.

Age-matched, full-term children with normal ocular findings were recruited from the Nara Medical University Hospital and the nursery school of the Tokushima University Hospital for the control group. Children with myopia greater than − 1.00 diopter (D) or with hyperopia greater than + 2.00D were excluded. In addition, children with organic eye diseases, history of intraocular surgery, cataract, glaucoma, or any retinal disorders, and those who could not cooperate with the OCT examination were excluded. One eye per patient was randomly selected for analysis.

All patients and controls were examined using slit-lamp biomicroscopy, extraocular motility assessment, subjective cycloplegic refractions (1% cyclopentolate and 2.5% phenylephrine), dilated ophthalmoscopy, and SD-OCT imaging. The same examination procedures were used for both eyes of patients with ROP and the right eyes of the controls. One eye per patient was randomly selected for analysis.

The retinal thickness, axial length, and BCVA of 18 eyes of the control patients have been reported.[27–29] The visual acuity was measured using a standard Snellen chart at 5 months and was converted to the logarithm of the minimal angle of resolution (logMAR) units for statistical analyses. The axial length was measured with IOL Master (Carl Zeiss Meditec, Jena, Germany) and AL-2000 (TOMEY, Nagoya, Japan). The refractive error (spherical equivalent), gestational age, birth weight, sex, and history of laser treatment were also evaluated.

Measurements of retinal layer thickness

The retinal layer thickness was determined using SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany; Cirrus SD-OCT, Carl Zeiss Meditec, Jena, Germany and RS-3000, Nidek, Gamagori, Japan). The thicknesses of the fovea, IRL, ONL, and photoreceptor IS and OS layers were measured in the temporally scanned OCT images of the fovea. The thicknesses at 1 mm nasal and temporal to the fovea were also measured as the parafoveal thickness. The foveal depression was calculated by subtracting the central foveal thickness from the mean parafoveal thickness.

The thickness of each retinal layer was determined by two experienced retinal specialists who were blinded to the diagnosis. They evaluated the retinal thickness independently and manually using an open-access software ImageJ (version 1.50a; NIH, Bethesda, Maryland, USA). ONL thickness was measured as the distance from the outer border of the inner limiting membrane (ILM) to the external limiting membrane (ELM). IS length was measured as the distance between the ELM and outer border of the ellipsoid zone (EZ). OS length was measured as the distance between the outer border of EZ and the inner border of the retinal pigment epithelium (RPE). The arithmetic means of the two examiners were used for statistical analyses. The inter-observer reproducibility was evaluated using intraclass correlation coefficients (ICCs).

Statistical Analyses

The data are expressed as means ± standard deviation (SD). The gestational birth date, age at the time of the examination, BCVA, axial length, refractive error (spherical equivalent), and foveal structures of the ROP and control eyes were compared using one-way ANOVA with post-hoc Tukey tests. The presence of the inner retinal layer was compared using theχ^2-test. Univariate and multivariate linear regression analyses were performed to determine the significance of the correlations between BCVA and the foveal depression and IS thicknesses of ROP and control eyes. The potential confounders (gestational age, birth weight, axial length, laser treatment and ROP stage) were included in the multivariate linear regression analyses. The standardized coefficients (ß) were calculated for each independent variable. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using licensed statistical software (SPSS version 22.0; SPSS Inc., Chicago, IL, USA).

Declarations

Author Contributions Statement

T.N., T.U., Y.M. and N.O. wrote the manuscript.

T.N., K.S., N.K., A.M., T.K., S.O., and T.T. collected data. Y.M., F.G., M.N., M.O. and S.Y. revised the manuscript.

All authors reviewed the manuscript.

Competing Interests

The authors declare no competing interests.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, TN, upon reasonable request.

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Figures

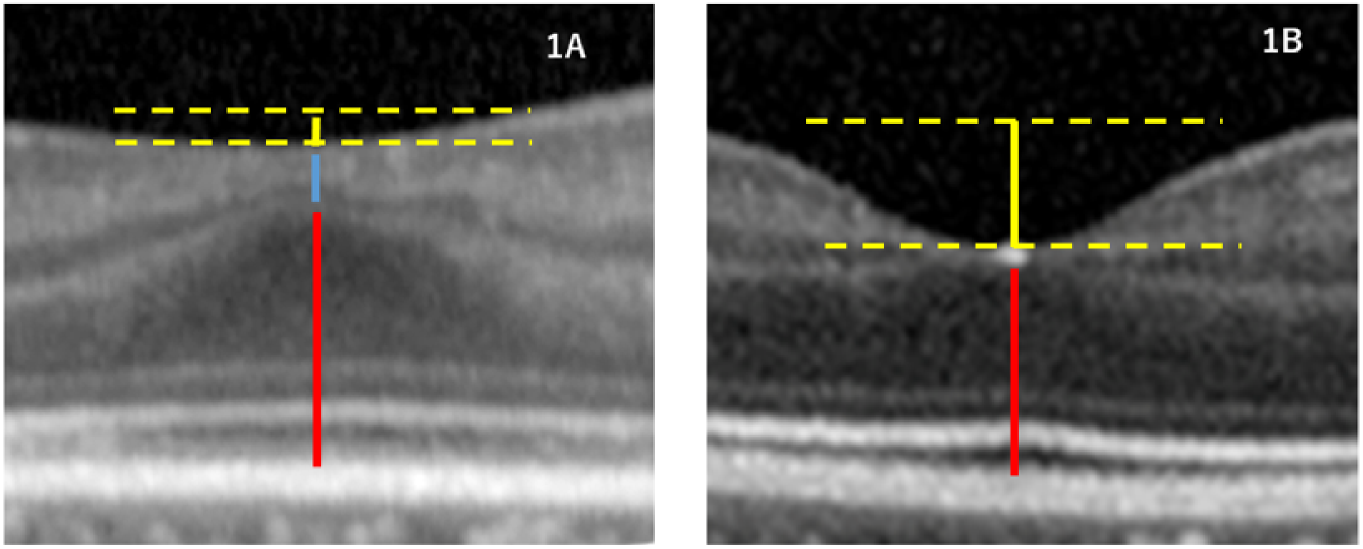

Figure 1

A: Optical coherence tomography (OCT) images of a representative patient with retinopathy of prematurity (ROP) who underwent laser treatment.

The foveal depression is shallow, at 22.5 μm in the OCT images, and IRL of the fovea is preserved (Figure 1A). The inner retinal layer (blue line) at the fovea is still present. The foveal thickness (inner retinal layer and outer retinal layer, i.e., blue line and red line, respectively) is 239 μm, and OS length is 40 μm. Yellow line: foveal depression; blue line: inner retinal layer; red line: outer retinal layer B**:** OCT image of a representative eye from the spontaneously regressed ROP group. The foveal depression is 108.5 μm in the OCT images (Figure 1B). IRL of the fovea is not detected and the foveal thickness (red line, outer retinal layer) is 237 μm. OS length is 43 μm. Yellow line: foveal depression, red line: outer retinal layer