

Retinal Sequelae in Adults Treated With Cryotherapy for Retinopathy of Prematurity

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PURPOSE. Cryotherapy, introduced in the mid-1980s, was the first treatment of severe retinopathy of prematurity (ROP) and resulted in ablation of larger retinal areas than did its later substitute, laser treatment. We defined the characteristics of the retinal structure and assessed visual function, in adult ex-preterms treated with cryotherapy.

METHODS. A total of 28 ex-preterms, included in a prospective study of infants born in Stockholm between September 1988 and March 1993, were treated with cryotherapy because of severe ROP. Of these individuals, 14 took part in this follow-up study and underwent ophthalmologic assessment including visual acuity, fundus photography, perimetry, and retinal imaging using optical coherence tomography (OCT) in their third decade of life. Their gestational ages were 24 to 28 (median 25) weeks at birth.

RESULTS. The ex-preterms had reduced foveal depth ($P < 0.0001$) and increased thickness of the temporal retinal nerve fiber layer (RNFL; $P > 0.001$). A thicker temporal RNFL was not correlated with a thicker ganglion cell layer ($P = 0.41$, $r = 0.29$) as in controls ($P = 0.0015$, $r = 0.78$). Extreme thickening was seen in patients with pronounced retinal dragging.

CONCLUSIONS. In their third decade of life, ex-preterm adults treated with cryotherapy for ROP have major microstructural retinal abnormalities in terms of reduced foveal depth and an altered distribution of the peripapillary RNFL. The main contributors seem to be gestational age and ROP rather than the cryotherapy. The possibility to evaluate the retinal structure in these individuals, with today's conventional OCT, is limited by those anatomic deviations.

Keywords: ganglion cell inner plexiform layer, cryotherapy, foveal microanatomy, retinopathy of prematurity, optical coherence tomography, gestational age

Retinopathy of prematurity (ROP) is a sight-threatening condition affecting 70% of extremely preterm born children.¹ In the 1980s, cryotherapy was recognized as a useful method to prevent blindness and later laser therapy became established as the standard treatment of ROP.^{2,3}

Treatment of severe ROP with cryo- and laser therapy has been successful in preventing total blindness. However, undesired outcomes, such as high myopia, retinal dragging, and retinal folds with poor visual acuity, still may occur despite treatment. Several microstructural changes associated with prematurity itself and with ROP have been recognized, based on examination with optical coherence tomography (OCT).

In ex-preterms, with and without ROP as well as treated and untreated ROP, arrested foveal development has been described. The single most important determinant for the degree of foveal maturation seems to be gestational age (GA) at birth.^{4,5} The typical anatomic alterations of the foveal anatomy are reduced foveal depth (FD) and incomplete extrusion of the inner retinal layers (IRL). The outer segments (OS) demonstrate less abnormality, independent of the abnormal maturation of the inner retina.⁶

Reduced retinal nerve fiber layer (RNFL) thickness also has been reported as a common finding in ex-preterms. Åkerblom et al.⁷ reported a thin RNFL in children with severe and treated ROP while no difference was found between children with no

or mild ROP compared to full-term controls. Wang et al.⁸ presented similar results and in addition they found reduced RNFL thickness in all quadrants but the temporal where the RNFL was significantly thicker compared to the controls.

Recently, another OCT-parameter has been introduced to describe the structural alterations in the macula after preterm birth. Pueyo et al.⁹ reported on the thickness of the ganglion cell complex (GCL_IPL thickness), including the ganglion cell layer (GCL) and inner plexiform layer (IPL) in the macula. They found that ROP-treated ex-preterms had a severely reduced minimum GCL_IPL thickness compared to controls, while there was no difference between the group of nontreated ROP infants and controls. They also reported that the laser treated ROP children had a thin RNFL in the superior and nasal quadrants and an increased RNFL in the temporal quadrant of the peripapillary RNFL.

Cryotherapy was the first treatment of severe ROP. To our knowledge there are no reports on the long-term impact of cryotreatment, in ex-preterm young adults, on retinal microstructure, in relation to visual function.

The aim of this study was to define the characteristics of the foveal and surrounding retinal structure in ex-preterm individuals treated with cryotherapy, and to assess visual functions, in the third decade of life.



MATERIALS AND METHODS

A total of 28 very-low birthweight (VLBW) infants, who took part in a prospective study of infants born in Stockholm between September 1988 and March 1993,¹⁰ were treated with cryotherapeutic retinal ablation because of severe ROP, with additional cerclage in two cases. Of these 28 subjects, 22 took part in a follow-up study of blood pressure and how it correlated with the retinal disease (Kistner A, Jacobson L, Östergren J, Hellström A, unpublished data). Visual function was assessed and the current retinal status was documented with fundus photography ($n = 21$) and OCT ($n = 14$) at a median age of 24.5 years (range, 22.5–26.5 years). In this study, we described the retinal morphology, and the objective and subjective visual outcome in those 14 individuals in whom satisfactory OCT results were obtained. These 14 VLBW individuals had GAs of 24 to 28 (median, 25) weeks at birth and birth weights (BW) of 550 to 1080 g (median, 870 g). Eight were female. All but one had a normal intellectual level. A history of subjective visual problems was sought.

Eight VLBW individuals were not examined with OCT. They had GAs of 24 to 30 weeks (median, 25) at birth and BWs of 571 to 1280 g (median, 744). Five of these eight had a learning disability. Two were severely visually impaired. These eight individuals had a best corrected visual acuity (BCVA) of 0.05 to 1.25 (median, 0.5) in the right eye, and 0.05 to 1.25 (median, 0.8) in the left eye. Refraction as spherical equivalent ranged between -18.5 and $+1$ D (median, -3.5) in the right eye and between -20 and $+1$ D (median, -1.75) in the left eye.

Control Group

A total of 13 young adults (10 females), coming for routine examination to the Optometry Clinic at the Karolinska Institutet, were included as control subjects. Inclusion criteria were birth at term, no history of ocular disease and absence of visual complaints. Median age was 25 years (range, 22–34). For the qualitative description of OCT and visual field (VF) outcomes, the normative database in the software was used, whereas data from the control group were used for the quantitative analysis of OCT and FD.

The study was approved by the local ethics committee and followed the tenets of the Declaration of Helsinki. All participants provided signed informed consent.

Fundus Photographs

Fundus photographs were obtained in all 14 individuals. Vascular dragging was classified as no, mild, moderate, or severe, by two experienced pediatric ophthalmologists.

Optical Coherence Tomography

Retinal scans were obtained by the use of the spectral-domain OCT from Carl Zeiss, model HD-Cirrus OCT 5000 version 8.0 (Carl Zeiss Meditec, Dublin, CA, USA).

The macular cube scan 512×128 , covering 6×6 mm of the retina with the fovea centered, was used for imaging the macular structure. One single macular B-scan was selected for further analysis. This horizontal scan was identified by using anatomic landmarks to ensure that the scan represented the foveal center (FC). Those landmarks were the foveal reflex when visible and/or where the maximum foveal depression was found, as well as the highest peaks of the foveal photoreceptor segment layer. The measure describing FD was defined as a ratio given in percentage. It was calculated as the difference between the retinal thickness at the foveal center and the mean retinal thickness of the temporal and nasal

rims at the foveal wall maximum. Retinal thickness was measured from the internal limiting membrane to the outer border of the RPE. The method has been described recently in detail.⁵

The RNFL thickness was mapped and measured with the Optic Disc Cube 200×200 protocol. The average RNFL thickness and RNFL in the four quadrants (i.e., superior, inferior, nasal, and temporal) were reported. The automatic comparison of RNFL thickness against the normative database was used for classification into normal (including borderline values) or abnormal values.

The perifoveal GCL thickness was estimated by analyzing the GCL_IPL complex (including the GCL and IPL), as performed automatically by the OCT software program (ganglion cell analysis). Mean and minimum GCL_IPL thicknesses were registered.

High image quality of the OCT measurements was defined as images with small or negligible influence by eye movements and/or blinking, and signal strength 6 or higher.

Descriptive Grading of Foveal Development

The inner part of the retina was evaluated by estimating the foveal pit formation/FD and extrusion of the IRL in the FC. The FD was classified as normal when the distance between the fovea wall maximum and the RPE was approximately 30%.⁵ In a fully mature fovea there is no sign of the IRL in the absolute center. Therefore, incomplete extrusion of the IRL at the fovea center was taken as a sign of immaturity. The outer part of the retina was characterized by observing the presence (normal) or absence (abnormal) of the three hyperreflective bands; the external limiting membrane, inner segment (IS)/OS boundary, and inner border of the RPE complex, together with a peak formation, that is, protuberance of the ellipsoid zone of the photoreceptor layer at the FC.

Descriptive Grading of RNFL Structure

The RNFL thickness was graded against the normative database incorporated in the OCT machine. Thickness values are indicated as “within normal limit” (within 5%–95% of normal distribution), “borderline” (within 1%–5% of normal distribution), or “outside normal limit” (within 0%–1% of normal distribution), respectively. In this study, values classified as “outside normal limit” were identified and classified as reduced RNFL-thickness. The average RNFL-thickness and average thickness within the four quadrants were graded.

Visual Field

Standard automated perimetry was used for quantitative measurement of VF defects with the SITA Fast 24-2 test (Humphrey Field Analyzer; HFA; Carl Zeiss Meditec). Results were expressed as the mean deviation (MD), an overall value of the total amount of VF impairment. For visualization of the relation between structure and function, the VF defects, given as pattern standard deviation (PSD), were plotted against the RNFL structure by using the analyze-tool, Combined reports_HFA_24-2_RNFL, from Carl Zeiss Meditec FORUM program version 2.0.4.33 (Fig. 1).

Statistics

Unpaired *t*-tests with Welch correction were used for comparisons between groups. The Spearman rank correlation was used for correlation analyses. Bonferroni correction was used to compensate for the multiple analyses presented in the Table. The significance level was set to a *P* value of 0.004, that

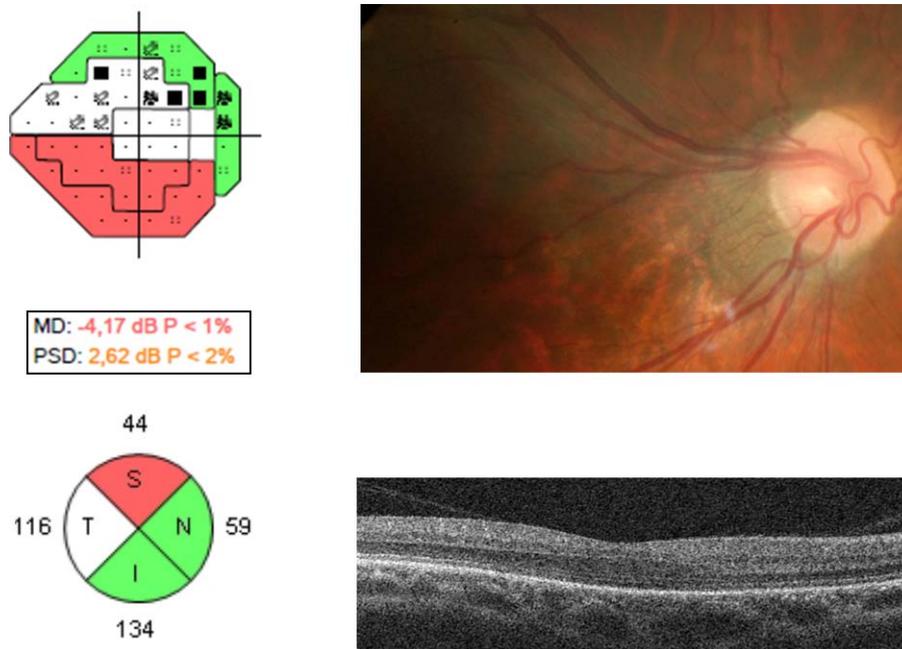


FIGURE 1. Case presentation of an adult treated with cryotherapy for ROP. This Figure presents a typical case for the ex-preterm group. *Top left* shows the VF defects plotted against the corresponding RNFL. *Red color* indicates retinal areas with thin RNFL, *white color* an extra thick RNFL, and *green values* within normal as compared to the age-matched control material integrated in the software. No association between retinal structure and function can be seen. Mean deviation and PSD values are presented in the *box* below the VF printout and given as decibels. *Bottom left* shows the peripapillary RNFL thickness in the four quadrants. Typical for the ex-preterm group was an extra thick temporal RNFL and thinning in either the superior (as in the case presented) or inferior quadrant. The most pronounced temporal RNFL thickening was associated with severe dragging resulting in reduced arcuate shape and straightening of the vessels, as seen from the fundus photo *top right*. Another common finding was reduced FD or absence of a foveal pit and incomplete extrusion of the IRLs at the fovea center as seen on the OCT scan, *bottom right*. The color code *green, yellow, and red* means: “within normal limits” (within 5%-95% of normal distribution), “borderline” (within 1%-5% of normal distribution), and “outside normal limits” (within 0%-1% of normal distribution). *White* means values thicker than within the normal distribution (i.e., supranormal values).

is, *P* value of 0.05 divided by the number of analyses (0.05/12 = 0.004).

RESULTS

History of Subjective Visual Problems and Ocular Complications

Of the 14 ex-preterms, one was visually impaired, with a decimal BCVA of 0.2 in the right and left eyes. In the group,

decimal BCVA ranged from 0.15 to 1.25 (median, 0.8) in the right eye and 0.1 to 1.6 (median, 0.8) in the left eye. Refraction, calculated as the spherical equivalent, ranged between -6 and +1.5 D (median, -3.5) in the right eye and -10 and +2.0 D (median -2.75) in the left eye. Four individuals complained of floaters. Two had photophobia. One had problems to focus at near. Two complained of episodes of a colored patch described as a central scotoma in the VF during and after physical training. Two had had vitreous hemorrhages, and had

TABLE. RNFL Thickness and FD in Adult Ex-Preterms Treated With Cryotherapy for ROP and Controls

	Ex-Preterms Right Eyes, <i>n</i> = 14	Ex-Preterms Left Eyes, <i>n</i> = 13	Controls, <i>n</i> = 13	<i>P</i> Value	
				Right Eyes	Left Eyes
Average RNFL thickness, μm	99.4 ± 15.2	100.9 ± 18.5	97.2 ± 8.8	NS	NS
Inferior RNFL thickness, μm	128.9 ± 30.5	115.5 ± 39.8	129.1 ± 14.2	NS	NS
Superior RNFL thickness, μm	93.1 ± 32.2	107.2 ± 30.6	120.0 ± 10.5	NS (<i>P</i> = 0.01)	NS
Nasal RNFL thickness, μm	62.3 ± 12.8	68.5 ± 21.6	77.7 ± 12.8	NS (0.005)	NS
Temporal RNFL thickness, μm	113.4 ± 36.1*	105.2 ± 33**	61.9 ± 9.2	(<i>P</i> = 0.0001)	(<i>P</i> = 0.0005)
FD ratio, %	9.1 ± 10.0*	10.3 ± 10.8**	34.9 ± 4.1	(<i>P</i> < 0.0001)	(<i>P</i> < 0.0001)

Data are presented as mean values ± SD. Right and left eyes of the ex-preterm group were compared separately to eyes of the control group. NS, not significant; FD ratio, the difference between the retinal thickness at the foveal center and the mean retinal thickness of the temporal and nasal rim at foveal wall max.

* Bonferroni corrected *P* value was used counteract the problem of multiple comparisons and the significance level was set to *P* ≤ 0.004. However, *P* values below 0.05 are noted in the Table.

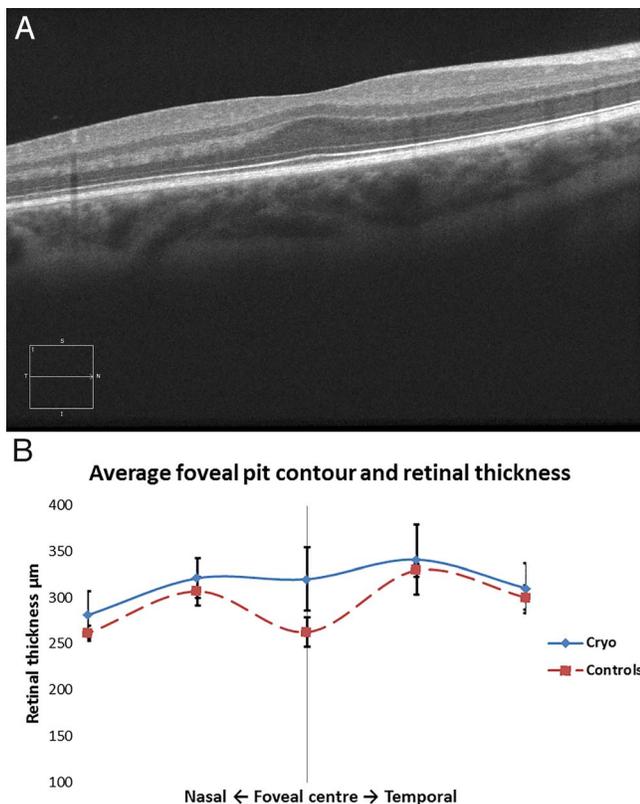


FIGURE 2. (A, B) Arrested foveal development in an adult ex-preterm treated with cryotherapy for ROP. *Top image* in (A) shows typical foveal appearance within the study group, including ex-preterm individuals treated with cryotherapy for ROP. This subject was born in GW 27, suffered ROP stage 3, and underwent cryotherapy (right eye). The FD is shallow and there is a substantial rest of nonmigrated IRLs in fovea center. Despite this, three hyperreflective bands of the outer retina, that is, the external limiting membrane, IS/OS boundary, and the inner border of the RPE, are visible. There also is a well-defined OS peak formation in the foveal center and the structure appears normal. *Bottom image* in (B) shows average retinal thickness, as measured with the macular cube scan and foveal pit contour. *Blue line* indicates ex-preterms treated with cryotherapy and *red line* indicates controls. Thickness values are given as mean and SD (*black lines*).

undergone vitrectomy. One had sustained severe uveitis in one eye leading to lens extraction and vitrectomy.

In one subject the OCT measurements could not be performed due to nystagmus and one case was excluded from correlation analysis between FD and GCL_IPL owing to macular scarring after uveitis.

Among controls median BCVA was 1.5 (range, 1.0–2.0) and spherical equivalent -0.25 D (range, -5.25 to $+1$).

Case Report

Figure 1 shows the fundus photograph, macular OCT scan, and VF plotted against the corresponding RNFL structure from a typical case in the ex-preterm group.

Fundus Photographs

In the group of ex-preterm individuals, 12 eyes had no, three had mild, four moderate, and nine had severe retinal dragging causing straightening of the vessels. In six eyes a pale and whitish layer spreading from the temporal side of the optic disc toward the macula was noticed. In these eyes a supranormal nerve fiber layer thickness was measured in the temporal

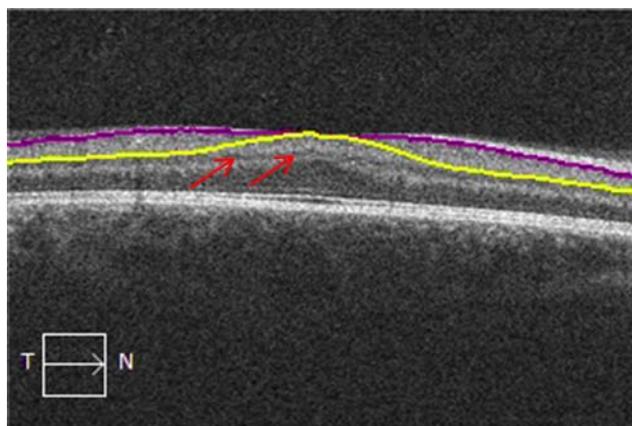


FIGURE 3. Segmentation of GCL_IPL as done automatically by the OCT software program in an ex-preterm treated with cryotherapy. The Figure shows the segmentation of the GCL plus IPL (GCL_IPL) as done automatically by the OCT software. *Purple border* indicates the border between the RNFL and the GCL, that is, the inner border of the GCL_IPL. *Yellow line* indicates the border between the IPL and the IRL, that is, the outer border of the GCL_IPL layer. The *red arrows* indicate the true border of the outer border of the GCL_IPL layer. This error frequently occurred in eyes with incomplete extrusion of the IRL in the foveal center.

quadrant of the peripapillary nerve fiber layer, for example see Figure 1.

Foveal Development

In all but two subjects the FD was abnormal. Both subjects with a normal foveal pit formation had discrete IRL remaining in the FC, together with a normal appearance of the OSs. A total of 12 subjects had a reduced FD or near absent pit formation, incomplete extrusion of IRL with a normal appearance of the OSs in both eyes (for example see Fig. 2, high resolution OCT image of the fovea). One subject did not have signs of an OS/IS-peak formation, but the three reflective bands could be distinguished, see Figure 1. The appearance was similar in both eyes.

RNFL Structure and GCL Thickness

All 14 subjects showed normal (11) or supranormal (3) average RNFL-thickness. Eleven subjects had a supranormal RNFL-thickness in the temporal quadrant in one (3) or both (8) eyes. Six subjects had a markedly reduced RNFL-thickness in the superior (most frequently occurring) or inferior quadrant. In these cases the extra thick temporal RNFL balanced the reduced thickness seen in other quadrants, since they had normal average RNFL thickness.

The ganglion cell analyze software program failed to reveal the true borders of the GCL_IPL layer in several of the ex-preterm eyes with incomplete extrusion (see Fig. 3). The error resulted in some extreme deviations of the minimum GCL_IPL thickness values. The mean values also were falsely reduced.

Visual Field

An example of VF outcome, that is, PSD and MD, is presented in Figure 1. Nine subjects had a MD below 1% in relation to the normative data base in both eyes, three subjects in one eye, and two were classified as within normal limits in both eyes. The extent and degree of sensitivity reduction did not show any specific pattern typical for the group and did not correlate with the RNFL structure. Three subjects had binasal defects,

not correlated with the RNFL structure but in one subject the VF defect was correlated with the retinal locations of the scars from cryotherapy. Median MD was -3.4 dB (range, -0.32 to -9.18) in the right eye and -3.5 dB (range, -0.34 to -8.14) in the left eye.

Quantitative Data

In comparison with controls, the group of ex-preterms, treated with cryotherapy for ROP, had reduced FD and thicker RNFL layers in the temporal peripapillary quadrant. The GCL_IPL layer was successfully segmented in one or both eyes in 7 of 14 ex-preterms (totally 10 eyes). When comparing this subgroup to the control group, no significant difference was found (mean difference, -3.52 , $P = 0.22$ and confidence interval [CI] $[-9.3-2.3]$).

In the control group, a thicker temporal RNFL was correlated with a thicker GCL_IPL layer ($P = 0.0015$, $r = 0.78$); such a relation was not seen in the small group of ex-preterm subjects with reliable GCL_IPL thickness values ($P = 0.41$, $r = 0.29$).

No correlation was found between BCVA and FD or between the VF MD and average or temporal RNFL thicknesses. Neither was there a correlation between FD and temporal RNFL thickness.

DISCUSSION

In this follow-up study of 14 ex-preterm individuals in their third decade of life, treated with cryotherapy for ROP and examined with OCT, we found reduced FD or absence of a foveal pit, incomplete extrusion of the IRLs at the fovea center, and increased thickness of the temporal RNFL. Similar deviations have been found in subjects treated with laser photocoagulation for ROP.^{6,9,11} Another important finding was the difficulties in the automatic analysis of the GCL_IPL thickness in the macular area.

Reduced FD is a well-described phenomenon in preterm infants.^{7,12} In the present study, six of 14 subjects were qualitatively graded as having absence of a foveal pit. Wu et al.,⁶ who studied a group of ex-preterm children with similar demographics regarding GA and ROP as in our study and treated with either laser or cryotherapy, reported an incidence of absent foveas in almost 90% of the cases. In an earlier publication by Recchia and Recchia,¹³ including untreated ROP eyes and ROP eyes treated with cryotherapy, 7 of 20 (35%) cases had absence of a foveal depression. One could speculate if the cryotherapy was a major factor leading to the absence of a foveal depression. On the other hand it should be noticed that all of our subjects with absence of the foveal depression were born extremely preterm (GW 24–26). Gestational age has been recognized as the main determinant for foveal maturation in a previous study in which the variables ROP, ROP-treatment, and degree of prematurity were partly adjusted for.⁵ In addition to GA, it is likely that the dragging caused by the ROP, also contributes to the reduced FD.

Regarding the outer retinal segment, the three hyper-reflective bands were noticed in all subjects. However, in one subject the IS/OS-peak was poorly developed and undetectable. Altogether, this finding of a well-developed OS is in line with previous studies.^{5,6}

The results of the RNFL measurements were surprising. After preterm birth and cryotreatment for ROP, the RNFL thickness could be expected to be reduced, as found by others.^{7,11} Instead, all our subjects had a normal or supranormal average RNFL thickness. However, in 10 subjects, a significant contribution to the average RNFL thickness came

from the temporal quadrant which was supranormal, while the quantitative analysis indicated a thinner RNFL thickness in the superior and nasal quadrants in right eyes. Severe ROP leads to dragging of the retina toward the temporal periphery with stretching of the arcuate temporal vessels compressing the retinal tissue between the upper and lower vessel arc. Then, retinal dragging in ROP is a result of the organization and contraction of the primary vitreous. This process is likely to cause thickening of the temporal RNFL.

Abnormal composition of the axons, including glial cells as described by de Juan et al.¹⁴ or collagen matrix as suggested by Woo et al.¹⁵ has been observed after ROP treatment. It cannot be excluded that such tissue contributes to the thickness. Another interfering factor could be the interruption of the normal apoptosis of retinal axons and ganglion cell migration. This process is intense between GW 16 and 32,¹⁶ and an interruption may have promoted an abnormal distribution of the axons.

It can be questioned whether the OCT can differentiate true nerve fibers from gliosis or collagen and, although we did not find any errors in the segmentation of the RNFL, we must strongly recommend critical interpretation of all OCT images in this group of individuals.

During measurement of the GCL_IPL complex, we revealed some fundamental difficulties. In eyes with incomplete extrusion of the IRL at the foveal center, the software was unable to recognize the true borders of the GCL_IPL layer resulting in extremely low and erroneous thickness values. Another possible explanation is the design of the measurement protocol. The size of the inner ring (used in ganglion cell analysis) was chosen originally to exclude the most central foveal area where the IRLs are absent in normally developed foveas. The outer ring was chosen to conform closely to the normal macular anatomy, where the GCL is thickest in normal eyes.¹⁷ The eyes we measured are not normal and the deficient migration of the ganglion cells might have resulted in falsely low thickness values.

The analysis of the small number of eyes with reliable GCL_IPL measurements in the ex-preterm group did not differ from the controls. The strong association between the temporal RNFL thickness and GCL_IPL thickness among controls, however, was not seen in the ex-preterm group. The absence of such correlation in the cryotreated group might support the abutment that the OCT is unable to differentiate healthy axons from dysfunctional tissue.

In a previous report, an extra thick temporal RNFL combined with reduced GCL_IPL was observed in a group of young ex-preterms treated with laser therapy.⁹ We suggest that the relation between supranormal thickening of the temporal RNFL and decreased GCL_IPL thickness must be questioned further.

Reduced VF sensitivity was seen in all but one subject in our group. The VF defects did not correlate with the RNFL structure and did not show any specific patterns typical for the group. Most subjects had undergone VF examinations before, but a few of them were novice, which may have influenced the result.

Our data did not show any correlations between visual acuity and foveal structure, nor did we find any correlation between the VF function and RNFL thickness. The relation between visual structure and function appeared complex in this study group. Recently, an extreme relationship was demonstrated in a group of ex-preterms without history of ROP treatment but suffering from white matter damage of immaturity.¹⁸ In that study, the RNFL was predicted by the damage to the optic radiation. The appearance of the RNFL structure in our study group is more likely to be explained by the history of severe ROP.

Altogether, the foveal pit formation is closely linked to GA at birth while the thickening of the temporal RNFL showed a closer relationship to retinal dragging. All eyes were treated with cryotherapy, but dragging was seen only in some. Therefore severe ROP, rather than the treatment, seems to affect the retinal nerve fiber distribution and to some extent the FD.

The study was limited by the small number of individuals who could be examined with OCT. The use of statistical methods is strongly limited by the small number of participants. Therefore, the result on a group level should not be applied to individuals. Neither can the study group be regarded as representative of the whole group of individuals who needed treatment for severe ROP, as they, as a group, had better intellectual and visual function than those who were not examined with OCT.

CONCLUSIONS

In their third decade of life, ex-preterm adults treated with cryotherapy for ROP have major microstructural retinal abnormalities in terms of reduced FD and an altered distribution of the peripapillary RNFL. The main contributors seem to be GA and ROP rather than the cryotherapy. The possibility to evaluate the retinal structure in these individuals, with today's conventional OCT, is limited by those anatomic deviations. The combination of subnormal visual function, visual complaints, and retinal abnormalities may, later in life, make the detection of age-related pathology difficult.

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