Understanding Clinically Undetected Macular Changes in Early Retinopathy of Prematurity on Spectral Domain Optical Coherence Tomography

Anand Vinekar, Kavitha Avadhani, Munusamy Sivakumar, Padmamalini Mahendradas, Mathew Kurian, Sherine Braganza, Rohit Shetty, and Bhujang K. Shetty

Purpose. To investigate macular changes in acute retinopathy of prematurity (ROP).

Methods. Fifty-four premature infants with ROP and 20 controls underwent routine ROP screening with indirect ophthalmoscopy and imaging. A tabletop spectral domain optical coherence tomography (SD-OCT) scanner (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was converted into a handheld device to image infants in the office sans sedation.

Results. SD-OCT images were obtained in all infants in the office. On SD-OCT, 23 of 79 eyes (29.1%) with stage 2 ROP showed abnormal foveal changes despite clinically normal foveae. Of the 23 eyes, 2 distinct patterns of foveal involvement were observed: "pattern A," which was characterized by dome-shaped foveal elevation and cystoid spaces with highly reflective intervening vertical septae, and "pattern B," which was characterized by preservation of the foveal depression with fewer intraretinal cystoid spaces. These patterns were seen in 12 (52.2%) and 11 (47.8%) eyes, respectively. All eyes (100%) belonging to stage 1 ROP (27) and the normal group (40) had no abnormal SD-OCT changes. The mean central foveal thickness was 156.9 ± 28.3 μm, 206.5 ± 98.7 μm, and 135.9 ± 17.6 μm for stage 1, 2, and normal eyes, respectively ($P < 0.001$). Nineteen of the 23 eyes underwent serial imaging at 52 weeks' postmenstrual age (PMA), and all of them revealed normalization of foveal contours at this visit.

Conclusions. SD-OCT changes of the macula in mild ROP have not been previously described. Our method reveals that infants may be imaged supine and unanesthetized in the office. We hypothesize that these transient foveal changes at the critical time of fovealization in premature infants may influence their visual acuity in the adult life. (*Invest Ophthalmol Vis Sci.* 2011; 52:5183–5188) DOI:10.1167/iovs.10-7155

The current criterion standard for retinopathy of prematurity (ROP) diagnosis, indirect ophthalmoscopy, is being constantly improved by innovations in wide-field digital imaging (WFDI) which allows for better understanding of this disease.[1–4] Important in this armamentarium is optical coherence tomography (OCT), which has helped us better understand the subclinical findings that are clinically relevant in the management of ROP.[1–3]

Pediatric OCT imaging has been limited chiefly because of the limitations of the available machines in imaging the uncooperative child. The child is either required to sit upright and co-operate during the examination, or the procedure must be performed in the operating room under anesthesia.[1,2,5–7] Spectral-domain (SD) OCT allows for higher-resolution images that can be acquired faster and more accurately compared to time-domain (TD) OCT, and therefore has a theoretical advantage in imaging children.[1,8–11] Recently, the availability of a handheld SD-OCT (Bioptigen Inc., Research Triangle Park, NC) has allowed us to overcome the disadvantages of an office-based tabletop system.[3,8–10] Most studies thus far have required the child sedated or under anesthesia and are often performed in the operating room.[3,6,8] We described a technique using a modified handheld device to capture SD-OCT images of non-anesthetized infants with ROP in the office, converting a conventional tabletop device, the Spectralis Heidelberg Retina Angiograph + OCT (Heidelberg Engineering, Heidelberg, Germany).[12]

Recently, the advantage of SD-OCT in the management of three cases of advanced ROP after the detection of features such as preretinal structures, retinoschisis, and retinal detachment not identified on standard examination has been highlighted.[3]

The morphologic changes of acute ROP in the earlier stages have not been reported. Interestingly, despite the spontaneous resolution of most cases of mild ROP, these have been shown to possess structural and functional disruptive changes in the fovea years after disease resolution.[13] The study of OCT changes in this early period of life may help us better understand these late changes. We also hypothesize about the possible role of our findings in influencing visual acuity in adulthood.

To the best of our knowledge, our study shows central foveal changes in the acute, early stages of ROP imaged on SD-OCT for the first time. We hypothesize the clinical implication of our findings based on what is known from studies on the foveal neurovascular development in preterm neonates.[14–16]

Materials and Methods

Patients

This study was approved by the institutional review board of our institute and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the parents or legal guardians of all the infants imaged. Fifty-four Asian Indian infants with ROP and 20 controls were included. The cohort of infants included in this study was derived from 22 neonatal care centers spread across Southern

From the Narayana Nethralaya Postgraduate Institute of Ophthalmology, Bangalore, India.

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Corresponding author: Anand Vinekar, Department of Pediatric Retina, Narayana Nethralaya Postgraduate Institute of Ophthalmology, 121/C, 1st R Block, Rajajinagar, Bangalore 560010, India; anandvinekar@yahoo.com.

Karnataka, South India. These centers are screened by pediatric retina specialists in an outreach program managed by our institute. This program uses teleophthalmologic principles and the use of WFDI and Internet transfer of images to remotely situated experts.

The infants of consenting parents were scheduled for SD-OCT imaging at our base hospital. WFDI using the Retcam Shuttle (Clarity MSI, Pleasanton, CA) was performed at each screening visit and before obtaining the SD-OCT images and were saved using the image protocol described by the PHOTO-ROP group.[17,18] Fundus examination at the time of OCT imaging was performed using an indirect ophthalmoscope by one of the authors (AV). Controls were obtained from infants who had no ROP in both eyes at any time during their screening protocol. Eyes were categorized by the worst stage of ROP that it developed during any visit. This also coincided with the stage of ROP at the time of imaging. At our institute, we review all infants undergoing ROP screening at 52 weeks' postmenstrual age (PMA). Therefore, the OCT scans were all repeated at 52 weeks' PMA.

Converting the Spectralis to A Handheld Device

The method used to obtain SD-OCT images has been recently described by our group.[12]

In our novel modification, we disassembled the camera unit from the base by removing the M6 Allen screw from the rotational bearing at the bottom of the arc guide. With this, the camera head turns free and is supported by holding the camera handle at the back of the mount and gently lifting it off the base of the instrument.

Infants were wrapped in sheets with their heads exposed. An atraumatic wire infant speculum and topical anesthesia (proparacain 0.5%) was used to open one eye at a time. The camera was brought in alignment with the infant's dilated pupil. When the point of interest was visible on the screen, the movement of the camera was minimized by the operator who had steadied his hand resting on an armature. The horizontal or vertical green line present on the infrared (IR) screen was then moved manually using the mouse cursor and placed over the exact point of interest by an assistant. The assistant also captured the images using the touch panel of the device.

Throughout the procedure, an assistant kept the corneas hydrated with frequent instillation of lubricants (Refresh Tears; Allergan, Irvine, CA). A single drop of topical antibiotic (Tobrex 0.3%; Alcon, Fort Worth, TX) was placed in the conjunctival sac at the end of the procedure. The infant was also monitored by an attending pediatric anesthetist for potential systemic problems.

The entire procedure could be completed in the office without sedation. A pacifier soaked with a few drops of dextrose (10%) was used during the procedure. No child needed intubation, intravenous medication, nasopharyngeal mask medication, or general anesthesia. The procedure would be completed within 10 minutes in each case. All infants who underwent OCT imaging were observed in the daycare unit of our institute by the pediatric anesthesia team. No systemic or ocular side effects were noted during or immediately after the procedure.

Selecting Images for Analysis

Images were reviewed by two observers masked to both Retcam images and stage of ROP, and the best quality images were accepted for the study. Categorization of images into ROP stages were also performed by masked experts because at our institute we follow a teleophthalmologic model with remote reading in addition to on-site clinical examination. We were not able to obtain volumetric scan in most cases because of the motion artifacts of the unanaesthetized infant. Therefore, the horizontal section (line) scan was used in this analysis.

In the absence of volume or raster scans, thickness was measured using default settings that demarcate the retina and measures the thickness. Default horizontal markings on the Spectralis correspond to the internal limiting membrane (ILM) superiorly and a hyperreflective line corresponding to the RPE/Bruch's junction (basement membrane [BM]) inferiorly. A line transects the scan vertically and runs through the center of the scanned image by default. While ascertaining the central foveal thickness, we moved the default vertical line to coincide with the presumed foveal center in cases where the foveal pit or depression was obvious. In cases where the foveal center was disrupted and there was increased foveal thickness suggestive of edema, the default marking would be moved to coincide with the height of the foveal dome. The horizontal lines were also moved to correspond to the ILM superiorly and BM inferiorly when the default lines failed to do so. The height in microns (μm; the distance between the two horizontal lines) was read off from the displayed value. This value was tabulated for central foveal thickness analysis.

Statistical analysis was performed for the difference of means using parametric tests with SPSS software (version 12; SPSS Inc., Chicago, IL).

Results

One hundred forty-six eyes of 74 Asian Indian infants were included in the study. One hundred six eyes were detected to have ROP, while 40 eyes were those of premature infants that never had any ROP in any visit. All infants were screened until they had normal vascularized fundi in both eyes.

For the purpose of this analysis, the infants have been grouped as no ROP (n = 40 eyes), stage 1 ROP (n = 27 eyes), and stage 2 ROP (n = 79 eyes). The three groups were comparable at baseline with respect to birth weight ($P = 0.65$), gestational age ($P = 0.145$), and postmenstrual age ($P = 0.949$) at OCT imaging and are detailed in Table 1.

There were 27 eyes with the highest stage of stage 1, 79 eyes with highest stage of stage 2, and 40 eyes with no ROP. The mean central foveal thickness of these three groups was 156.9 ± 28.3 μm, 206.5 ± 98.7 μm, and 135.9 ± 17.6 μm for stage 1, 2, and the eyes with no ROP, respectively. The macular thickness between the three groups was significant $P < 0.001$. On post-hoc test, the difference was related to stage 2 ROP (normal vs. stage 2, $P < 0.001$; stage 1 vs. stage 2, $P = 0.012$).

Retrospective analysis of the OCT scans revealed abnormal foveal changes in 23 of the 79 eyes (29.1%) with stage 2 ROP. All eyes with no ROP and those with stage 1 ROP showed no morphologic abnormalities in the foveal center or the macula on any of the SD-OCT imaging sessions. The central foveal changes were categorized into two subtypes for this study. The

Table 1. Baseline Characteristics of Infants Enrolled during ROP Screening for SD-OCT Imaging Using the Spectralis Device

	Stage 1 ROP	Stage 2 ROP	Normal	*P*
No. of eyes (*n*)	27	79	40	
Sex ratio (M/F)	8/6	22/18	10/10	
Birth weight, g (mean ± SD)	1332.86 ± 288.99	1247.43 ± 237.80	1269.58 ± 324.00	0.650
Gestational age, wks (mean ± SD)	32.36 ± 2.68	30.91 ± 2.12	31.25 ± 2.32	0.145
Postmenstrual age at OCT imaging, wks (mean ± SD)	37.04 ± 2.69	37.18 ± 1.95	37.10 ± 2.79	0.949

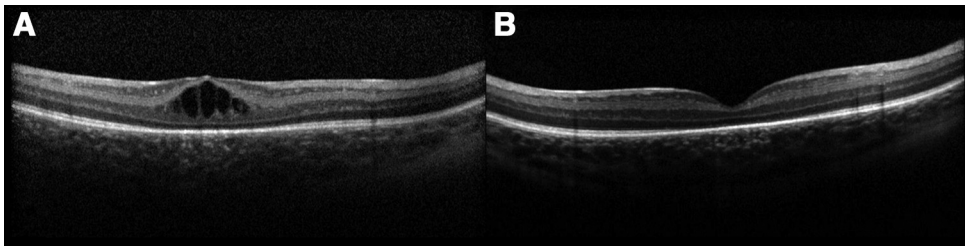

FIGURE 1. (**A**) "Pattern A" foveal changes seen in a female infant with stage 2 ROP, imaged at 37.3 weeks' postmenstrual age. The macula was normal ophthalmoscopically. These SD-OCT changes resemble "cystoid macular edema" of adults and feature a dome-shaped elevation in the center of the fovea accompanied by intraretinal cystoid spaces with highly reflective intervening vertical septae between the roof and floor of the dome with complete disruption of the foveal depression or pit in all cases and accompanied by a marked increase in central foveal thickness. (**B**) Normal foveal contour was restored by 52 weeks' postmenstrual age.

two subtypes are based only on the OCT appearance that we noted, with no prejudice as to the severity of one compared to the other. Clinical correlation of these changes was limited by the fact that all eyes had normal foveae and maculae ophthalmoscopically and on digital imaging.

The first type of foveal change, "pattern A," had a dome-shaped elevation in the center of the fovea that resembled classical cystoid macular edema in adults. This was accompanied by intraretinal cystoid spaces with highly reflective intervening vertical septae between the roof and floor of the dome with complete disruption of the foveal depression in all cases and accompanied by a marked increase in central foveal thickness (CFT). The second morphologic type, "pattern B," featured multiple confluent or near confluent vacuolated optically empty or hyporeflective spaces within the layers of the retina with no obvious or few septae, an almost normally preserved foveal depression, and moderately increased CFT.

The distribution of patterns of foveal disruption that we used to categorize these changes (patterns A and B) were seen in 12 (52.2%) and 11 (47.8%) eyes, respectively (Figs. 1 and 2). All eyes had normal foveae clinically at all visits.

The CFT in all stage 2 ROP eyes was 206.5 ± 98.7 μm. Eyes with stage 2 ROP with normal morphologic foveae on OCT ($n = 56$) had a mean CFT of 158.9 ± 37.6 μm. The 23 eyes with abnormal foveae on OCT had a mean CFT of 315.5 ± 109.3 μm. The mean CFT of pattern A (12) and pattern B (11) eyes was 406.8 ± 72.2 μm and 224.1 ± 39.8 μm respectively ($P < 0.001$).

From this cohort of 12 infants with abnormal OCT scans, 10 (83.3%) underwent repeat scans at 52 weeks' PMA, and two infants could not be contacted. These 10 infants contributed 19 eyes of stage 2 ROP to the cohort. All 19 eyes (100%) showed a normalization of foveal contours at 52 weeks' PMA irrespective of the preceding pattern of abnormality. Eyes underwent a mean of 2.3 serial OCT imaging sessions during their ROP follow-up (Table 2).

One female infant (birthweight 1200 g, period of gestation 32 weeks) had stage 1 ROP in the right eye and stage 2 ROP in the left eye. The eye with stage 2 ROP showed pattern A foveal changes which resolved at the 52-week PMA follow-up, whereas the eye with stage 1 ROP had normal macula on OCT at both visits (Fig 3).

DISCUSSION

Despite the widespread use of OCT in adult vitreoretinal diseases, its application to the pediatric population has been limited chiefly because of the limitations in the availability of machines in imaging the uncooperative child. Children have been imaged on OCT either in the supine position or under anesthesia in the operating room[1,2,8–10]

The utility in detecting subclinical pathologies has been established previously with the use of the TD-OCT[1,2] and more recently with the SD-OCT.[3,12,19,20] TD-OCT, for instance, has shown that ROP stage 4A with macular sparing was in fact 4B undetected by clinical examination. This would influence the surgical consideration and outcome of these infants. Chavala et al.[3] recently revealed that the handheld SD-OCT (Bioptigen Inc., Research Triangle Park, NC) showed preretinal structures, retinoschisis, and retinal detachments in three infants with severe ROP that were undetected by experts using standard examination techniques. The potential for detecting subclinical pathology using this new technology seems to be improving with the use of adaptive optics including Fourier-domain OCT[13] and by a more recently described protocol used to optimize the parameters of the handheld OCT device by Maldonado et al.[19]

To a large extent, the availability of the handheld SD-OCT (Bioptigen Inc.), which provides two- and three-dimensional SD-OCT scans with a resolution of better than 10 μm, has helped image infants.[20] However, this device is also limited by the requirement of a very skilled operator, clear media, and a still infant. Moreover, reliable and reproducible images with the handheld SD-OCT can be technically challenging.[20]

We recently described a method that converts a tabletop combined imaging device (Spectralis) into a handheld device to image the supine, nonanesthetized infant in the office set-

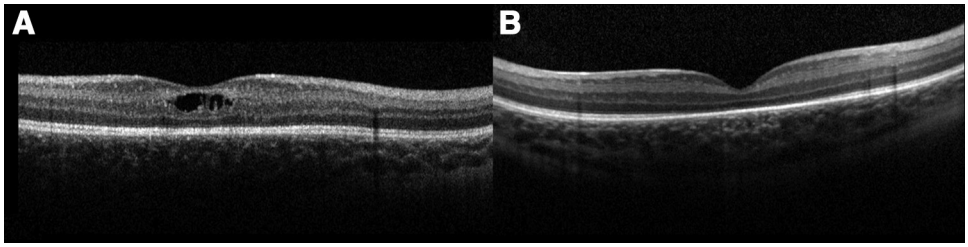

FIGURE 2. (**A**) "Pattern B" seen in a male infant with stage 2 ROP with a normal macula on ophthalmoscopy imaged at 38.1 weeks' postmenstrual age. This pattern is characterized by multiple confluent or near confluent vacuolated optically empty or hyporeflective spaces within the layers of the retina with no obvious or fewer septae, an almost normally preserved foveal depression or pit, and moderately increased central foveal thickness. (**B**) Normal foveal contour was restored by 52 weeks' postmenstrual age.

Table 2. Distribution of Abnormal Foveal Changes (Stage 2 ROP) Detected on SD-OCT in Ophthalmoscopically Normal Fundi and Imaged on the Retcam during ROP Screening

Serial Number (Sl. no.)	Birth Weight (g)	Period of Gestation (wks)	Corrected Age (Postmenstrual) at OCT Imaging (wks)	Pattern of Foveal Change	No. of Follow-Up OCT Visits	Final Outcome
1	1200	26	42	B	2	Normal fovea at 52 weeks' PMA
2	1200	30	37	A	3	Normal at 52 weeks' PMA
3	950	30	38	A	2	Normal fovea at 52 weeks PMA
4	1040	29	35	A	4	Normal fovea at 52 weeks' PMA
5	1400	32	38	B	1	—
6	1460	32	41	A*	2	Normal fovea at 52 weeks' PMA
7	1320	32	39	B	2	Normal fovea at 52 weeks' PMA
8	1300	29	36	B	3	Normal fovea at 52 weeks' PMA
9	1360	32	46	A	3	Normal fovea at 52 weeks' PMA
10	1250	28	36	B	2	Normal fovea at 52 weeks' PMA
11	1000	30	35	B	3	Normal fovea at 52 weeks' PMA
12	1370	34	41	A	1	—

* One eye with stage 2 ROP exhibited pattern A; the other eye had stage 1 ROP and had normal fovea on SD-OCT (not included in this table).

ting. We showed that images could be obtained from the same area of interest serially and demonstrated its utility in mapping clinically missed flat neovascularization in cases of acute aggressive posterior ROP.[12] In this series, we show the utility of the same procedure in imaging the macula of infants with mild ROP.

It is noteworthy that none of the 40 control eyes or the 27 eyes with stage 1 ROP showed any foveal disruption or edema. More than a quarter (29.1%) of cases with stage 2 ROP revealed foveal changes. We chose to classify these changes into two types with no prejudice to grade them according to the severity. The pattern A changes, comprising loss of foveal depression and a dome-shaped serous elevation was noted in 12 (52.2%) of these eyes. Pattern B or cystic changes within the retinal layers with preservation of the normal foveal contour was noted in 47.8%. More interestingly, we noted that of the 19 eyes with abnormal OCT changes imaged at 52 weeks' PMA, all (100%) normalized at this visit. However, we could not obtain serial images this late (PMA) in the remaining eyes included in the study, and in those we did image at 52 weeks' PMA, we were not able to determine the exact week of normalization because weekly SD-OCT images were not possible.

The etiology of these macular changes, especially the "edema" that resembles adult cystoid macular edema, is currently unknown. Although we did not find any neonatal risk factor(s) to be significantly distributed between the three groups, it is possible that unique comorbid factors may influence the disease pattern in our setting, which may influence structural changes in the macula, especially in the heavier infants screened in our country. This may not be applicable to

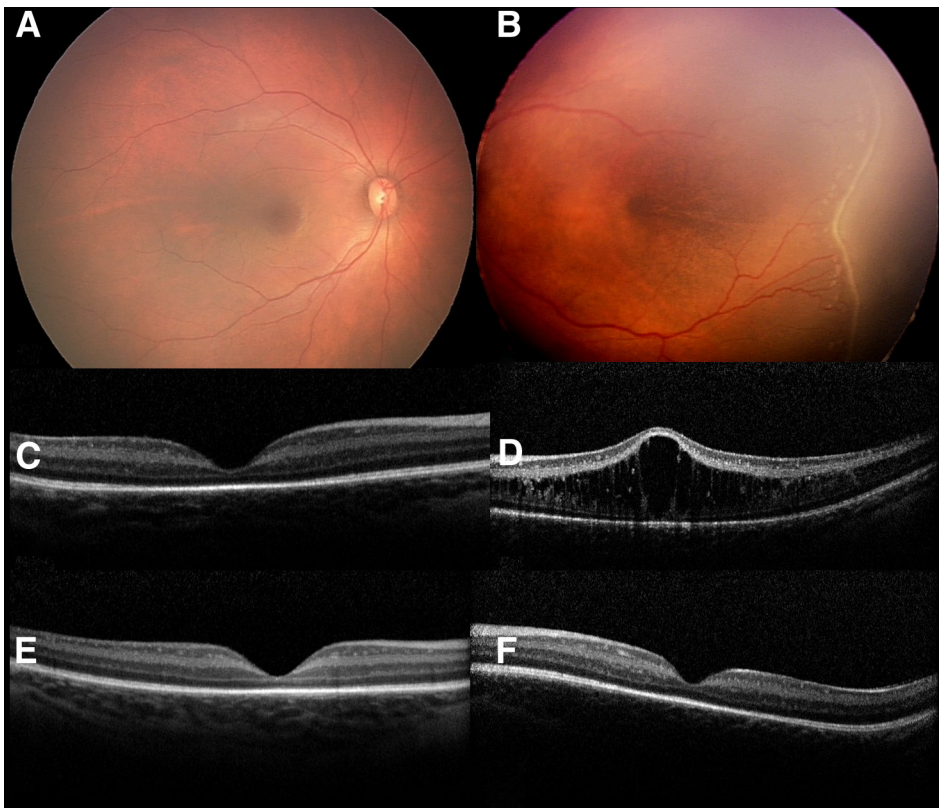

Figure 3. A female infant weighing 1200 g at 32 weeks' gestation was serially screened for ROP. At 37 weeks' postmenstrual age, she developed stage 1 ROP in zone two anterior in the right eye (**A**; line of demarcation not seen in the photograph) and stage 2 ROP in zone two posterior (**B**; seen as the ridge). The stage 1 eye showed no macular/foveal changes on SD-OCT (**C**). The left eye with stage 2 ROP showed "pattern A" foveal changes (**D**). Both eyes had normal fovea on SD-OCT at 52 week' postmenstrual age (**E** and **F**).

other countries where these heavier infants are not at similar risk.[21,22] In the absence of any obvious causes for the macular edema, we hypothesize that this "macular edema" seen in eyes (29.1%) with more severe ROP could either be (1) a response to biochemical modulators, including higher concentrations of vascular endothelial growth factors (VEGFs), which could play a role in increased vascular permeability leading to retinal edema, or (2) could be caused by mechanical traction exerted on the macula. The biologic plausibility and rationale of the hypothesis of the biochemical theory has been suggested in retinal vascular disorders including AMD, diabetic retinopathy, retinal artery or vein occlusion, and ROP.[23] This is further corroborated in cases of stage 4 ROP and more advanced disease wherein VEGF was observed in much higher concentrations in the vitreous compared to controls.[24] In a study of 27 cytokines in the vitreous of ROP cases, VEGF was found to have the strongest correlation with vascular activity in the disease.[25] Studies correlating early ROP (stages 1 and 2) with vitreous levels of these cytokines are not available because of the difficulty in obtaining samples from these early cases. However, it is probable that levels in "excess of normal" contributing to increased permeability in the retinal vessels begin at these early stages and could be responsible for the macular changes we have observed. However, it must be emphasized that this theory currently remains speculative, because there is insufficient evidence to suggest that VEGF is significantly different between cases of stage 1 and 2 ROP.

With regard to the mechanical theory, there is currently insufficient evidence to believe that the "ridge" (stage 2) may contribute to mechanical traction that may extend to the fovea being greater in volume than the "line of demarcation" (stage 1) to explain the foveal changes on OCT. However, this has been implicated in stage 4A ROP, where OCT has shown the separation or schisis-like change to extend more posteriorly, converting a diagnosis of 4A to stage 4B.[2] To summarize, we are unsure at this time of the exact etiology of the foveal edema in some and not in others. Our theories remain speculative and at best may serve to encourage additional research on this subject.

The findings of this study also allow us to extend our understanding of the development of the premature fovea to hypothesize the possible clinical and long-term effects of these abnormal changes. Anatomic studies on the development of the premature fovea have revealed that the formation of a parafoveal avascular zone occurs by midgestation, a period that coincides with the birth of subjects with ROP.[26,27] Later in gestation, there is a widening of the foveal pit with elongation of the cone inner and outer segments, and closer cone–cone packing that occurs and continues after birth and into early childhood.[14–16] In formation of the ROP fovea, the centrifugal forces that lead to pit widening may not be intimately linked to the centripetal forces that lead to cone packing.[13] In addition, growth factors, including VEGF, neuropilin, and semaphorin, have been shown to have a role in the ROP fovea.[28,29]

Adaptive optics Fourier-domain OCT (AO-FDOCT) on older individuals with historically mild ROP was reported by Hammer et al.[13]They observed neurovascular abnormalities in seven of nine cases (77.8%), and the authors opined that mild ROP may not universally contribute to long-term changes. Years after suffering from mild ROP, these cases presented with degraded best corrected acuity attributed to mild optical aberration or metabolic effects on neural cells that are sensitive to contrast. It was also suggested that the loss of foveal cones or increased cone–cone spacing were also responsible for these visual changes. Interestingly, it was noted that there was no paucity of cones years later despite the fact that cone packing may have been affected. We hypothesize that the transient edema in 29% of our cases may contribute to abnormalities in cone packing without affecting the actual number of cones by causing increased physical separation between adjacent cones that may hinder their tight packing during this critical period of immaturity—namely, between 37 and 52 weeks' PMA.

However, it must be emphasized that correlating vision in adults with historical ROP with macular changes is currently speculative in the absence of long-term follow-up studies. Clinically, the vision of young adults with historical ROP may be less than[13] or better than[30] predicted from the appearance of the macula. Studies of adults also suggest that vision may be altered by changes described as a vestige of prematurity, including changes in foveal depression, hyporeflectivity, preserved retinal layers, increased central foveal thickness, and total macular volume measured on TD- OCT.[31] Cellular level changes and histologic evidence suggest that intraretinal separation in the inner retinal layers account for increased retinal thickness in patients with macular heterotopias, which correlates with reduced visual acuity.[32] In addition, OCT in adults with historical ROP presenting with relatively normal maculae clinically has revealed a loss of foveal depression, increased macular thickness, and continuation of inner retinal layers within the fovea.[33] A small or absent foveal avascular zone[34] and attenuated central retinal ERG responses to multifocal stimulation in children[35]with historic ROP helps us hypothesize about the long-term effects of early macular changes described in the study. However, only long-term studies can conclusively help us understand the relevance of these early changes. Although the changes resolve by 52 weeks' PMA, it is uncertain if permanent effects may have set in by this time.

There are several other limitations of this study. First, the retrospective nature prevents serially documented OCT changes week after week in the acute period. This would give us a better understanding on the linear progression or regression of the macular changes. Second, we noted that these patterns of foveal edema resolved by 52 weeks' PMA. It is possible that the fovea normalized earlier, but because we schedule our infants at the third month of corrected age (approximately 52 weeks' PMA), this may bias the timing of our finding. Third, Raster scans to determine the volumetric distribution was not possible because this system is incapable of retinal tracking and because the image quality of these scans is poor. This limitation has also been noted in young adults with ROP even with advanced AO-FDOCT.[13] Line or section scans were possible with our method, even though the infant was not anesthetized. Other important limitations include the laterally inverted images because of the position of the operator in relation to the position of the infant. Motion artifacts were common, but were reduced with increasing practice. The procedure does, however, require a skilled operator who must adjust the mobile camera unit to reduce motion artifacts. The lack of a mount for image stabilization is a limitation. It must be noted that the Spectralis OCT machine was probably not intended for pediatric use, and our modification must be viewed in that light.

To the best of our knowledge, this is the first study that has reported subclinical changes on SD-OCT in the fovea in the acute ROP period in ROP that did not require treatment. We propose that these macular changes in the early premature period, although transient, could be the basis of future macular and foveal architectural changes reported in older ROP survivors,[13] contributing to the unexplained poor vision in these patients. Additional research is required to confirm this.

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