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Functional Outcomes of Young Infants with and without Macular Edema

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Summary Statement

Infants who showed age-appropriate retinal microanatomy on spectral domain optical coherence tomography imaging obtained in the nursery had age-appropriate visual acuities on follow-up as toddlers or school-aged children. By contrast, infants with macular edema on imaging, subsequently demonstrated suboptimal vision, sensorimotor deficits, brain abnormalities, and/or poor neurodevelopment.

Purpose—We relate posterior segment microanatomy from perinatal spectral-domain optical coherence tomography (SDOCT) to visual acuity (VA), brain abnormalities, and neurodevelopment.

Methods—Thirteen infants (11 preterm, 2 term birth), imaged in the nursery with portable SDOCT, had VA and sensorimotor testing at age 9–15 months (grating acuity) or 4–5 years (optotype), and medical records reviewed for brain magnetic resonance imaging (MRI) reports and Bayley Scales testing at age 18–24 months.

Results—Eight children with age-appropriate macular microanatomy without edema on perinatal SDOCT had optimal ($\geq 20/40$) or within normal limits (grating acuity) VA. Five children with perinatal macular edema had suboptimal VA (in 9/10 eyes) and either sensorimotor deficits, MRI abnormalities or poor neurodevelopment. Macular edema persisted in one infant through 9 months corrected age.

Conclusion—Maturation of the visual system and evolution of retinal anomalies can be monitored with posterior segment SDOCT. Retinal microanatomy observed in infancy might relate to subsequent vision as well as other central nervous system events, but additional studies

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are needed to determine the range of normal microanatomy in infants and how this relates to vision and neurodevelopment.

Keywords

Bayley scales; cystoid macular edema; development; macula; retinopathy of prematurity; infant; magnetic resonance imaging; optical coherence tomography; visual acuity; visual function

Purpose

The development of the visual pathway is a dynamic process of molecular and cellular interactions in the eye and brain with development of neural structures, circuit formation, signaling and function over time.¹ Environmental interactions including oxygen exposure, and potentially genetic variations, influence the likelihood of aberrant retinal vascular development which can lead to retinopathy of prematurity (ROP).^{2, 3} Development of normal visual function depends on the correct timing and interaction of these many complex processes. Assessment and identification of the causes of vision loss in children, especially those with a history of very preterm (VPT, less than 32 weeks gestational age) birth, are often confounded by developmental problems of the eye and brain. There is limited research in microanatomic development and abnormalities within the prematurely born infant's retina and optic nerve which could impact acuity and reflect other central nervous system disturbances. Only recently has there been technology capable of facilitating noninvasive evaluation of neuronal structural components of the retina and the visual system in young infants. Our knowledge of microanatomic evolution of the retina and optic nerve during the critical period of neurovascular development when infants are in the intensive care nursery has expanded due to the pioneered use of bedside spectral domain optical coherence tomography (SDOCT) in the nursery.⁴⁻¹⁰ However, functional data regarding vision outcomes on children who had SDOCT imaging as neonates remains unreported.

We believe that microanatomic features in the retina and optic nerves of infants observed with SDOCT may serve as prognostic indicators of abnormalities in the complex processes of visual pathway development and thus may predict functional visual outcomes of these infants as toddlers and children. In particular, we hypothesize that infants with subclinical cystoid macular edema (CME) observed on neonatal SDOCT, may subsequently have worse vision outcomes than infants without CME. To our knowledge, this pilot study is the first report of potential relationships between perinatal SDOCT findings in the posterior segment and subsequent visual acuities (VAs), which may relate to sensorimotor abnormalities, brain abnormalities, and neurodevelopmental outcomes.

Methods

All infants, with parent or guardian written informed consent, were enrolled in the current analysis from several, prospective studies that were approved by the Duke University Institutional Review Board and adhered to the Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki. Infants were eligible for the current analysis if they had SDOCT imaging while in the intensive care nursery and VA was later assessed between 9 months and 5 years of age. In a more recent longitudinal study,

outpatient follow up was included in the research protocol, while families of infants in earlier studies were contacted under an amended protocol to seek outpatient follow up.

At the discretion of the medical team, infants deemed clinically stable for research imaging underwent imaging of the posterior retina and optic nerve at the bedside with a portable, non-contact, hand-held SDOCT device (either an early Bioptigen research system or the Envisu, Bioptigen, Inc., Research Triangle Park, NC) at the time of clinically-indicated inpatient ophthalmic examinations (Video 1, Supplemental Digital Content, Handheld SDOCT Imaging of Infants in the NICU).^{4,5,11} One of two trained graders (A.L.R. or D.T.), masked to all patient information other than age at imaging, graded foveal SDOCT volumes using OsiriX v4.1.2 software (Pixmeo, Bernex, Switzerland). Each foveal scan was qualitatively assessed for presence of the ellipsoid zone (EZ) at the foveal center, cystoid macular edema (CME), and Vascular Abnormality Score on Optical Coherence Tomography (VASO), a sum of four component scores from OCT vascular grading (vessel elevation, hyporeflective vessels, perivascular spaces, and retinal layer scalloping) that are an SDOCT indicator of Plus disease.¹² Cystoid macular edema was considered present if there were one or more “hyporeflective round or elongated structure separated in most instances by a vertical hyperreflective band.”⁶ Any other additional abnormalities were also qualitatively described. Furthermore, central foveal thickness (CFT) and average foveal-to-parafoveal thickness ratio (FP ratio) at 1000 μ m from the fovea were measured from Bruch's membrane to the internal limiting membrane. One grader (A.L.R.) evaluated optic nerve cross-sectional B-scans using a custom MATLAB script (MathWorks, Inc., Natick, MA) described by Tong et al⁸ for vertical cup diameter, vertical disc diameter, vertical cup-to-disc ratio, and cup depth.

Infants returned for subsequent VA assessment and SDOCT imaging at either 9-15 months or 4-5 years corrected age. A trained orthoptist (S.H.) masked to all imaging, magnetic resonance imaging (MRI), ROP examination and neurodevelopmental data, evaluated sensorimotor function and VA with grating acuity by Teller Acuity cards (Vistech Consultants, Dayton, OH) for toddlers at 9-15 months and with the Amblyopia Treatment Study HOTV8 protocol on the Electronic Visual Acuity Tester for children at 4-5 years.¹³⁻¹⁵ Follow-up SDOCT imaging was obtained with Spectralis (Heidelberg Engineering, Heidelberg, Germany) for children ages 4-5 years or with the hand-held SDOCT device for toddlers at age 9-15 months (Video 2, Supplemental Digital Content, Handheld SDOCT Imaging of Infants in the Clinic). One of the two graders evaluated each follow-up scan for the same parameters as those used for evaluation of the SDOCT images taken while in the intensive care nursery. At the time of VA assessment, infant medical records were reviewed for basic demographic and medical information as well as assessment of neurologic health. Of note, research imaging data was not part of the infant's medical record and all other providers were therefore masked to this information. The medical record was reviewed for brain MRI radiology reports obtained while the infant was in the intensive care nursery as well as Bayley Scales of Infant and Toddler Development, Third Edition (Pearson, San Antonio, TX) assessments completed at 18-24 months corrected age in the developmental follow-up clinic. Bayley Scales assessments were performed by a licensed psychologist (K.E.G.) certified as a Bayley examiner by the National Institute of Health Neonatal

Research Network. Cognitive, language, and motor development scales are reported as standardized scores with a mean of 100 and standard deviation of 15.¹⁶

Results

A total of fifteen infants assessed with SDOCT while in the intensive care nursery underwent subsequent VA testing. Two of the 15 infants (both with abnormal SDOCT imaging and poor acuities) were excluded from the analysis due to retinal detachments and/or vitreous hemorrhages and surgery confounding the analysis, leaving a total of thirteen infants in this pilot study. One infant had a poor quality foveal SDOCT scan in one eye which could not be used to interpret foveal maturity or the presence or absence of edema. Infants 3, 5, 6, 9, and 11 had completed Bayley Scales of Infant and Toddler Development and were included in a previous study that related neonatal CME to neurodevelopmental outcomes.¹⁰ The optic nerve head parameters for one infant (#6, Table 1 and 2) were part of a larger report by Tong et al.⁸ Demographics, maximum ROP stage, finding of plus disease, laser treatment, and age at inpatient SDOCT imaging for the 13 infants are included in Table 1. Gestational age and birth weight for these infants ranged from 24 to 39 weeks post-menstrual age (PMA) and 542 to 3380 g, respectively, and seven infants had ROP higher than stage 0 (immature retina), three of whom had laser treatment. No infants received off-label bevacizumab.

Eight infants had what has emerged as age-appropriate perinatal SDOCT without edema while five infants had macular edema and one of these infants also had subretinal fluid in one eye. The normal macular microanatomy group had bilateral VA at or better than 20/40 (range 20/16 to 20/40) or age appropriate grating acuities on follow-up examination (Tables 1 and 2, “normal macular microanatomy group”, infants 1-8). The only child without CME who had 20/40 VA in each eye (infant 8) had 20/25 VA when the eyes were assessed together. The five children with macular edema on SDOCT had at least one eye with a VA of 20/40 or worse or grating acuities considered below the 99% nomogram for age (Tables 1 and 2, “macular edema group”, infants 9-13).¹⁵ Gestational age and birth weight ranged from 24-30 weeks PMA and 580-1060 grams in the normal macular microanatomy group and 24-39 weeks PMA and 542-3380 grams in the macular edema group, respectively. The normal macular microanatomy group had no retinal therapy for ROP, while the 3 of 5 infants in the macular edema group had bilateral laser treatment for treatment-warranted ROP.

Of the normal macular microanatomy group, four infants had age-appropriate indirect ophthalmoscopy exams without evidence of ROP, and four infants were diagnosed with stage 2 ROP without plus disease and other than the peripheral ROP findings, their retinal ophthalmoscopic examinations were normal. None of these infants had CME on SDOCT obtained in the nursery (Figure 1, top left). Central foveal thickness ranging from 146 to 238 microns and the VASO was 0 in ten eyes (6 eyes without ROP and 4 eyes with maximum Stage 2 ROP) and was 2 in five eyes (one eye without ROP and 4 eyes with maximum Stage 2 ROP). Two infants (# 4 and #6) had maturation of the EZ at the fovea while in the nursery. The optic nerve head cup-to-disc ratio in these eyes ranged from 0.4 to 0.9 and cup depth from 121 to 664 microns with no useful optic nerve images in three eyes (Figure 1, top

right). Infants 1-5 and 7 were imaged during outpatient follow-up examination. They all lacked CME and had bilateral, age-appropriate progressive development of photoreceptor outer segments as reflected by the progressive separation of the EZ from the retinal pigment epithelium (RPE) with progression of this separation into the foveal center. Three of the four children with stage 0 ROP also had inner retinal maturation with migration of inner retinal layers out of the foveal center while one of the two children with a history of stage 2 ROP who underwent follow-up SDOCT imaging had bilateral persistence of the inner retinal layers at the foveal center. None of these children had strabismus or amblyopia.

In the macular edema group, three of the five infants were preterm and had severe treatment-warranted ROP in both eyes. Infant 9 received laser treatment prior to enrollment in the study and had CME noted on both post-laser, in-patient imaging sessions. Infants 12 and 13 were imaged with SDOCT before and after laser treatment at 35 and 36 weeks PMA, respectively. Although after laser treatment the vascular changes reversed on indirect ophthalmoscopic examination (resolution of plus disease) and by VASO (decrease in score), their macular edema persisted in both eyes for multiple months. One infant also demonstrated two spots of focal non-macular, vitreous hemorrhage that persisted for 5 weeks after laser treatment, one spot above the optic nerve and one on the inferior posterior pole, outside of the macula along with a crescent of edematous nasal zone II retina that persisted for 3 weeks after laser.

Two of the three ROP infants with edema had adrenal insufficiency and both of the macular edema infants who were born at term had other complex health problems, one had liver failure from neonatal hemochromatosis and the other had hydrocephalus and pituitary insufficiency. The infant with liver failure (#10, Tables 1 & 2) was previously described by Maldonado et al.¹⁷ No vessel abnormalities were noted on indirect ophthalmoscopy, although a cherry red spot was suspected in both eyes. SDOCT demonstrated severe CME in the right eye and parafoveal subretinal fluid with early foveal pit development in the left eye and vascular abnormalities in both eyes by VASO (scores 5 and 3, respectively). Subsequent perinatal SDOCT revealed persistence of CME in the right eye and new severe CME in the left eye. After liver transplantation, and on systemic immunosuppression, the bilateral macular abnormalities promptly resolved. At his 4 ½ year eye examination, SDOCT revealed bilateral normal foveal pit formation with well-developed EZ at the fovea. The infant with hydrocephalus and panhypopituitarism (#11, Tables 1 & 2) had bilateral optic nerve hypoplasia noted on indirect ophthalmoscopy, though the vertical disc diameter was 1866 microns on SDOCT in one eye. Perinatal SDOCT revealed severe, bilateral CME present at both imaging sessions (Figure 1, bottom left). The right eye had a shallow cup depth of 191 microns on SDOCT and while the left optic nerve parameters could not be measured on SDOCT due to image tilt, it appeared very shallow (Figure 1, bottom right).

For all five macular edema infants, perinatal CFT ranging from 221 to 754 microns when edema was present, often with severe VASO even in eyes without ROP. The optic nerve head cup-to-disc ratio in these eyes ranged from 0.62 to 0.94 and cup depth from 191 to 503 microns with no useful optic nerve images in four of ten eyes.

In follow up examination at 9 months or later, 4 of 7 eyes imaged showed definite resolution of macular edema on SDOCT. In one VPT infant the macular edema was clearly still present in both eyes, not only at a clinic exam several months after leaving the nursery, but also through the 9 month corrected age examination. In another VPT infant, also examined at 9 months, there was a suspicious hyporeflectivity at the foveal center in one eye, which suggested CME (Figure 2). In 4 eyes there were persisting inner retinal layers at the fovea while 3 eyes had a normal appearing foveal pit. The EZ band was present at the foveal center in all eyes imaged. Four of the five macular edema infants had strabismus at follow up examination and one infant had strabismus surgery.

None of the normal macular microanatomy infants had brain MRI in their medical records and their medical records were only notable for preterm birth. Bayley cognitive, language, and motor development standard scores, obtained at 18-24 months corrected age, were available for the two infants with ROP and one without and demonstrated normal cognitive and motor development in all infants and mildly delayed language development in the two infants with ROP (Table 2).

Four of five macular edema infants had brain MRI obtained while in the intensive care nursery, and there were brain abnormalities on each (Table 2). Bayley Scales in two of the macular edema infants suggested moderate to significant delays across domains of development in one and low normal cognitive development and very significantly delayed language and motor development in the other. Two infants were too young for 18-24 month testing, one had developmental delay noted in the medical record and the other had neurodevelopment consistent with corrected age.

Discussion

Spectral domain optical coherence tomography imaging of the posterior segment of infants' eyes has increased our understanding of macula and optic nerve development. By comparing the microanatomy of preterm to full term infant eyes, we can identify delay and abnormalities in the intricate processes of ophthalmic development that typically occur *in utero*.^{7-9, 18, 19} To our knowledge, this is the first report that relates SDOCT findings of the posterior retina and optic nerve in infants to corresponding subsequent assessment of visual acuity. The eight infants with age-appropriate microanatomy on perinatal SDOCT had subsequent VAs at or better than 20/40 or within the normal limits on grating acuity using Teller Cards. As an aggregate, these infants had relatively normal Bayley scores. None of them had brain MRIs obtained, suggesting that brain imaging was not felt to be clinically indicated by their health care team. By contrast, the five infants with structural abnormalities noted on perinatal SDOCT, specifically bilateral CME, subsequently developed suboptimal VAs often associated with sensorimotor abnormalities on follow-up examination. Additionally, all of these infants either had brain abnormalities documented on MRIs obtained by their clinical team while in the intensive care nursery or subsequently had subnormal neurodevelopmental outcomes at 18-24 months. Because the optic nerve was imaged inconsistently in these infants in the original pilot study, identification of optic nerve development or abnormalities and subsequent associations with VA and brain development are limited. This study, however, points to the complex interplay between retinal and brain

development and possible abnormalities, a topic which warrants further study. A novel and concerning finding in this study was the persistence of bilateral CME for at least 11 months after onset, in a toddler with documented subnormal acuity and strabismus.

The etiology of perinatal CME, a relatively common finding in VPT infants who are screened for ROP, and the role it may play in vision development remain speculative.^{6,10,17,20,21} As in adult macular edema, there may be very different etiologies that produce this same anatomic event. Cystoid macular edema in two term infants with significant health problems, liver failure in one and hypopituitarism and hydrocephalus in the other, demonstrate that CME is not only associated with preterm birth. A recent study demonstrated that children with a history of CME in the nursery had worse language and motor skills as well as a trend towards worse cognitive outcomes than those without CME as an infant.¹⁰ Presence of CME after laser photocoagulation in three infants suggests that CME may not be a strictly vascular endothelial growth factor-mediated mechanism. Dubis et al.²¹ also reported CME following laser photocoagulation and persisting after bevacizumab administration. While some of the CME (also known as macular edema of prematurity) in the VPT infants may be partly driven by vascular endothelial growth factor dysregulation, the edema may reflect other inflammatory pathways in the fully vascularized retina of term infants and in some preterm infants.

It is difficult to differentiate the extent to which abnormal eye microanatomy and impaired neurologic health have contributed to maturation of the visual pathway. For example, infant 10 developed 20/25 vision in his previously edematous right eye while his amblyopic left eye had a history of both CME and subfoveal fluid, and a follow-up VA of 20/50. While healthy full-term children may have a small pocket of subfoveal fluid that persists in the first month after birth,²² it is uncertain whether this child's more diffuse subretinal fluid may have played a role in development of the sensorimotor abnormality. Additional longitudinal research is required to further describe how CME in preterm infants may affect vision and sensorimotor outcomes.

Few data exist regarding the relationship between retinal morphology on SDOCT and vision outcomes in the young pediatric population. This is of great interest in preterm infants, since 65% of those laser treated for ROP in the Early Treatment of ROP Study had subnormal acuity at school age, even though they often had a normal macular appearance on ophthalmoscopy. These children were not evaluated with SDOCT imaging.²³ Villegas et al.²⁴ found that persistence of the inner retinal layers at the fovea in school-aged children with a history of ROP does not impact VA but the few children with absence of outer segment elongation had VA worse than 20/40. Photoreceptor integrity on SDOCT is also implicated to correlate with vision outcomes in children after vitreoretinal surgery.²⁵ Persistence of inner retinal layers at follow-up SDOCT imaging did not seem to play a role in this study. Two infants with good VA had persisting inner retinal layers (infants 4 and 5) while another infant with fovea plana (infant 12) had poor acuity. Additionally, the presence of the EZ separated from the RPE at the fovea in infancy did not relate to corresponding subsequent vision outcomes as all children, regardless of perinatal SDOCT findings, subsequently had full development of the EZ with separation from the RPE. The height from

Bruch's to the EZ was not measured as this data would be difficult to compare in children at different endpoint ages.

As extensions of the central nervous system, the optic nerve and retina have long been recognized as a “window in to the brain.”²⁶ As such, posterior segment microanatomy observed on perinatal SDOCT may serve as biomarkers of neurologic health and have prognostic value for functional outcomes. For example, larger optic nerve cup-to-disc ratio measured on SDOCT in preterm infants have been correlated with poorer cognitive skills as a toddler, and infants with hydrocephalus (infant 11, Figure 1 bottom), have been reported to show shallower cup depths.⁸ Msall et al.²⁷ demonstrated that ROP severity is associated with neurodevelopment and even children of similar gestational age with favorable vision but with a history of more severe ROP have higher rates of functional deficits than those with less severe or no ROP. Retinopathy of prematurity may represent only one striking vascular aspect of a continuum of delayed and abnormal neurovascular development of the brain and retina in the VPT infant; for example, variants in the gene encoding brain-derived neurotrophic factor, were recently associated with severe ROP.² Perinatal systemic inflammation is associated with greater risk for brain injury and developmental disabilities and may also play a role in ROP and be reflected in CME.^{28,29} It is notable that all five infants with CME on perinatal SDOCT in the present study had either brain abnormalities noted on MRI or subsequent neurodevelopmental deficits. Cystoid macular edema may serve as a biomarker of central nervous system health. Additional research is required to evaluate how the relationship between perinatal CME observed in preterm infants in the intensive care nursery and vision outcomes are influenced by subsequent neurologic and developmental outcomes.

There were several limitations to this study. Because only thirteen infants who were imaged under the research protocols had follow-up VA assessed at a later date, this very limited population likely does not represent the balance of health and disease in the larger population. Optic nerve scans were available in only a minority of these eyes, as our early SDOCT imaging protocols prioritized macular imaging, limiting analysis potential. Some of the eye findings such as optic nerve hypoplasia (infant 11) were clinically apparent without SDOCT and may have impacted subsequent VA. Brain and neurodevelopmental abnormalities also likely impacted VA and thus CME on bedside SDOCT imaging may reflect the presence of these greater abnormalities rather than a direct retinal cause of subnormal acuity. This interrelationship is too complex to resolve with this pilot study population. Subsequent VA was only assessed at either 9-15 months or 4-5 years corrected age and so comparisons between VA at the two time points are limited. For example, one year grating acuity is recognized to be a limited predictor of optotype acuity at 5 ½ years age, although it is useful in distinguishing presence or absence of more severe subsequent visual impairment.³⁰ Follow-up SDOCT imaging was not possible in the clinic on all children during their follow-up visits due to their age and ability to cooperate. The brain MRI reports were performed only as clinically indicated by the treating neonatologist and did not consider the current research aims; thus, brain MRI imaging was not available on all infants.

Despite these limitations, this pilot study demonstrates that posterior retina microanatomy, especially macular edema, can be assessed by SDOCT in the intensive care nursery and later related to vision outcomes. Notably, all infants with age-appropriate perinatal SDOCT had subsequently normal VA as well as appropriate neurodevelopmental outcomes and no clinical indication for brain MRI imaging while in the intensive care nursery. In contrast, infants who had CME and other abnormalities noted on SDOCT subsequently developed suboptimal VA or sensorimotor deficits as well as brain abnormalities and poorer neurodevelopmental outcomes. These preliminary findings are from a limited dataset composed of subjects who returned for vision testing. While useful in pointing to possible areas for further research, the limitation should be recognized. Macular edema on SDOCT appears as a potential indicator of retinal or visual pathway function and potentially of global problems in early brain development. Prospective, longitudinal studies of infant SDOCT retinal imaging, brain MRI, visual acuity, and neurodevelopmental outcomes will likely be useful to identify ocular pathology that may influence subsequent visual outcomes in ROP and other neonatal conditions, and to begin to distinguish these from central nervous system causes of vision loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Spectral domain optical coherence tomography B-scans obtained from Infant 6 and 11 in the intensive care nursery

Top, Spectral domain optical coherence tomography (SDOCT) B-scans of the right eye of infant 6 at 41 weeks post-menstrual age. Subsequent visual acuity at 14 months was 4.8 cy/degree at 55 cm, within the accepted 99% normal limits for this age.¹⁴ Cognitive, language, and motor Bayley scores were 106, 77, and 97, respectively. **Top Left,** B-scan of the macula demonstrates age appropriate persistence of inner retinal layers with no lesions. **Top Right,** B-scan of the optic nerve. Optic nerve parameters are appropriate for a preterm infant as optic nerve cup and cup-to-disc ratio are typically larger for this population than full term infants.⁸ **Bottom,** SDOCT B-scans of the left eye of infant 11 obtained at 41 weeks post-menstrual age. At 14 months corrected age, visual acuity was 0.86 cy/degree at 55 cm in this eye, outside the accepted 99% normal limits for this age.¹⁵ Cognitive, language, and motor Bayley scores were 60, 74, and 55, respectively. **Bottom left,** SDOCT foveal B-scan demonstrates severe cystoid macular edema in the inner nuclear layer at the fovea with parafoveal cystoid spaces. **Bottom right,** SDOCT B-scan of left optic nerve of infant 8. The hypoplastic appearance of this optic nerve with no appreciated cupping is associated with hydrocephalus.⁸ Follow-up SDOCT imaging of the left macula at 14 months revealed normal development of the foveal pit and ellipsoid zone at the fovea as well as absence of any macular edema; the right eye was not adequately imaged for analysis.

Figure 2. Spectral Domain Optical Coherence Tomography B-scans of Infants 12 and 13

Top left, spectral-domain optical coherence tomography (SDOCT) B-scans obtained on the right eye of infant 12 at the last imaging session while in the intensive care nursery at 47 weeks post-menstrual age. Note the cystoid macular edema (CME) as well as persistence of inner retinal layers and lack of ellipsoid zone (EZ) at the fovea. **Bottom left**, follow-up SDOCT imaging obtained at 9 months corrected age of the right eye for infant 12 demonstrates resolution of CME with persistence of inner retinal layers as well as development and elongation of EZ from the retinal pigment epithelium (RPE) at the fovea. Neurologic history was notable for bilateral cerebellar and left parenchymal hemorrhage. **Top right**, SDOCT B-scans obtained on the left eye of infant 13 at the last imaging session while in the intensive care nursery at 42 weeks post-menstrual age. Note the CME causing foveal bulging as well as persistence of inner retinal layers and lack of EZ at the fovea. **Bottom right**, follow-up SDOCT imaging obtained at 9 months corrected age of the left eye for infant 13 reveals persistence of CME, although a shallow foveal pit is now appreciated. Also note the persistence of inner retinal layers as well as development and elongation of EZ from the RPE at the fovea. Neurologic history was notable for left cerebellar hemorrhage.

Table 1
Infant Demographics, Maximum Retinopathy of Prematurity (ROP) Severity and Age at Imaging

Patient	Gestational Age* (wks)	Birth Weight (g)	Sex	Race	Max ROP Stage [†]	Max Plus Disease [†]	Retinal Therapy [†]	Age (s) at Imaging* (wks)
1	30	1050	F	White	0	None	No	34
2	28	1060	F	White	0	None	No	32
3	28	720	F	White	0	None	No	33
4	26	640	F	Black	0	None	No	43
5	25	610	F	Black	2	None	No	31-35
6	26	710	F	Black	2	None	No	30-39
7	25	590	F	Black	2	None	No	44,46
8	24	580	M	Black	2	Pre-Plus	No	33-40
9	23	560	M	Black	3	None	Laser	41,43
10	39	1786	M	Black	NA	NA	No	43-46
11	38	3380	M	Black	NA	NA	No	41, 43
12	24	542	F	Multiple	3	Plus	Laser	32-40
13	24	590	F	Multiple	3	Plus	Laser	32-40

Wks, weeks; Max, maximum; ROP, retinopathy of prematurity; F, female; M, male; NA, not applicable

* Ages are reported as post-menstrual age for in-patient imaging

[†] Severity of ROP was symmetric in both eyes for each infant

Table 2
Perinatal Spectral-Domain Optical Coherence Tomography Findings and Magnetic Resonance Imaging and Functional Outcomes

Spectral Domain Optical Coherence Tomography In the Intensive Care Nursery																	MRI and Functional Outcomes				
ID	Eye	Age wks	Macular OCT	VASO ¹²	CFT µm	FP Ratio	EZ at Fovea	Cup Diameter µm	Disc Diameter µm	Cup- to-Disc Ratio	Cup Depth µm	Age	Visual Acuity	Strabismus	MRI Findings	Bayley Score Cognitive	Bayley Score Language	Bayley Score Motor			
1	OD	34	WNL	0	146	0.56	No	---	---	---	---	4.5 yr	20/20	No	---	---	---	---			
	OS		WNL	0	155	0.52	No	773	1527	0.51	335		20/20								
2	OD	32	---	---	---	---	---	---	---	---	---	4.5 yr	20/16	No	---	---	---	---			
	OS		WNL	0	175	0.76	No	1234	1323	0.93	463		20/20								
3	OD	33	WNL	2	165	0.65	No	1103	1336	0.83	494	4.5 yr	20/25	No	---	100	103	91			
	OS		WNL	0	144	0.62	No	1566	1993	0.79	585		20/25								
4	OD	43	WNL	0	238	0.77	Yes	930	1523	0.61	580	9m	4.7 cy/deg	No	---	---	---	---			
	OS		WNL	0	211	0.64	Yes	889	1482	0.60	453		3.1 cy/deg								
5	OD	35	WNL	2	224	0.86	No	880	2292	0.38	121	4.5 yr	20/25	No	---	95	74	94			
	OS		WNL	0	220	0.80	No	623	1221	0.51	258		20/32								
6	OD	41	WNL	2	155	0.57	No	1239	1904	0.65	554	14m	4.8 cy/deg	No	---	106	77	97			
	OS		WNL	2	165	0.66	No	1083	1455	0.74	664		4.8 cy/deg								
7	OD	46	WNL	0	216	0.66	Yes	840	1254	0.67	606	9m	3.1 cy/deg	No	---	---	---	---			
	OS		WNL	0	210	0.69	Yes	931	1402	0.66	649		3.1 cy/deg								
8	OD	38	WNL	2	150	0.40	No	---	---	---	---	4.5 yr	20/40	No	---	---	---	---			
	OS		WNL	0	146	0.42	No	---	---	---	---		20/40								
9	OD	41	CME	0	353	0.90	No	---	---	---	---	5 yr	20/63	Surgery for Esotropia w Hypertropia	---	85	68	52			
	OS		CME	0	351	0.84	No	---	---	---	---		20/40								
10	OD	46	CME	5	754	1.19	No	2026	2406	0.84	503	4.5 yr	20/25	Esotropia	Frontal lobe arteriovenous malformation	---	---	---			
	OS		CME SRF	5	702	1.31	Yes	1603	2604	0.62	502		20/50								

Spectral Domain Optical Coherence Tomography In the Intensive Care Nursery															MRI and Functional Outcomes			
ID	Eye	Age wks	Macular OCT	VASO ¹²	CFT µm	FP Ratio	EZ at Fovea	Cup Diameter µm	Disc Diameter µm	Cup- to-Disc Ratio	Cup Depth µm	Age	Visual Acuity	Strabismus	MRI Findings	Bayley Score Cognitive	Bayley Score Language	Bayley Score Motor
	OS		CME	2	515	1.73	No						0.9cy/deg					
12	OD	35	CME	5	228	0.95	No	1270	1404	0.91	348	9m	1.6 cy/deg	Esotropia	Cerebellar hemorrhage and atrophy, pons volume loss			
	OS		CME	2	226	0.97	No						0.3 cy/deg					
13	OD	35	CME	5	221	0.91	No	1417	1502	0.94	422	9m	1.6 cy/deg	No	Intraventricular and Posterior Fossa Hemorrhage			
	OS		CME	5	257	0.96	No	1330	1514	0.87	391		1.3 cy/deg					

MRI, magnetic resonance imaging; OCT, optical coherence tomography; ID, identification; VASO, Vascular Abnormality Score on Optical Coherence Tomography; CFT, central foveal thickness; FP, foveal-to-parafoveal thickness (average parafoveal thickness at 1000 µm); EZ, ellipsoid zone elongation from retinal pigment epithelium; WNL, within normal limits; U, unable to measure; CME, cystoid macular edema; SRF, subretinal fluid; yr, year; m, month; cy/deg: cycles per degree; w, with

Bold Visual acuity = 20/50 or worse on Snellen charts or outside the 99% accepted grating acuity for age on Teller cards¹⁴

Bold Bayley Score = subscale scores two or more standard deviations below the mean