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Authors

Mangalesh, Shwetha
Michalak, Suzanne
McGeehan, Brendan
et al.

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Associations between Systemic Health and Retinal Nerve Fiber Layer Thickness in Preterm Infants at 36 Weeks Postmenstrual Age

Liangbo L. Shen, MD[1], **Shwetha Mangalesh, MBBS**[2], **Suzanne M. Michalak, MD**[2], **Brendan McGeehan, MS**[3], **Neeru Sarin, MD**[2], **Joanne Finkle, RN, JD**[4], **Katrina P. Winter, BS**[2], **Du Tran-Viet, BS**[2], **Eric J Benner, MD, PhD**[4], **Lejla Vajzovic, MD**[2], **Sharon F. Freedman, MD**[2,4], **Noelle Younge, MD**[4], **C. Michael Cotten, MD, MHS**[4], **Mays A. El-Dairi, MD**[2], **Gui-shuang Ying, PhD**[3], **Cynthia A. Toth, MD**[2,5],

BabySTEPS Study Group

[1]Department of Ophthalmology, University of California, San Francisco, San Francisco, CA

[2]Department of Ophthalmology, Duke University School of Medicine, Durham, North Carolina

[3]Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania

[4]Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina

[5]Department of Biomedical Engineering, Pratt School of Engineering, Duke University, Durham, North Carolina

Abstract

Background/Aims: Neonatal insults from systemic diseases have been implicated in the pathway of impaired neurodevelopment in preterm infants. We aimed to investigate the associations between systemic health factors and retinal nerve fiber layer (RNFL) thickness in preterm infants.

Methods: We prospectively enrolled infants and imaged both eyes at 36 ± 1 weeks postmenstrual age (PMA) using a handheld OCT system at the bedside in the Duke intensive care nurseries. We evaluated associations between RNFL thickness and 29 systemic health factors using univariable and multivariable regression models.

Results: 83 infants with RNFL thickness measures were included in this study. Based on the multivariable model, RNFL thickness was positively associated with infant weight at imaging and was negatively associated with sepsis/necrotizing enterocolitis (NEC). RNFL thickness

Corresponding Author: Cynthia A. Toth, MD, Joseph A.C. Wadsworth Professor, Department of Ophthalmology, Duke University School of Medicine, 2351 Erwin Road-Suite 1002 AERI, Durham, NC 27710 (Phone: 919-684-5741, cynthia.toth@duke.edu).

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was 10.4 μm (95% confidence interval = −15.9 to −4.9) lower in infants with than without sepsis/NEC in the univariable analysis (P<0.001). This difference remained statistically significant after adjustment for confounding variables in various combinations (birth weight, birth weight percentile, gestational age, infant weight at imaging, and growth velocity). A 250-gram increase in infant weight at imaging was associated with a 3.1 μm (95% confidence interval = 2.1 to 4.2) increase in RNFL thickness in the univariable analysis (P<0.001).

Conclusions: Low infant weight and sepsis/NEC were independently associated with thinner RNFL in preterm infants at 36 weeks postmenstrual age. To our knowledge, this study is the first to suggest that sepsis/NEC may affect retinal neurodevelopment. Future longitudinal studies are needed to investigate this relationship further.

INTRODUCTION

The risk of major neurodevelopmental disabilities, including impaired cognitive and motor functions, hearing loss, and visual impairment, remains high (30–50%) in very preterm infants.[1] Neonatal insults from systemic conditions are significant contributors to impaired neurodevelopment in preterm infants. For example, systemic hyperinflammatory responses secondary to sepsis or necrotizing enterocolitis (NEC) may cause white matter injury and adverse neurodevelopment in preterm infants.[2 3] Poor postnatal growth in the neonatal intensive care unit (NICU), bronchopulmonary dysplasia, patent ductus arteriosus (PDA), and other systemic conditions are associated with long-term neurodevelopmental impairments in infants.[4–6] Besides, infants with more than 1 neonatal morbidity may have a cumulative risk of neurodevelopmental impairment.[7] Therefore, it is essential to identify biomarkers that can reflect systemic diseases' impact on the central nervous system in preterm infants, which may allow for timely evaluations and interventions.

Retinal nerve fiber layer (RNFL) consists of unmyelinated axons of retinal ganglion cells. Hence, optical coherence tomography (OCT)-measured RNFL thickness is a potential noninvasive biomarker for axonal injury, independent of myelination changes.[8] RNFL thickness serves as a clinical biomarker to diagnose and monitor congenital or acquired optic neuropathies (e.g., glaucoma and optic neuritis).[9 10] Thinner RNFL has also been associated with neuropsychiatric and systemic diseases in adults (e.g., systemic lupus erythematosus, Alzheimer's disease, and Parkinson's disease)[11–13] and children (e.g., optic pathway gliomas, type 1 diabetes, and severe obesity).[14–16] These findings demonstrate the potential value of RNFL thickness in managing adult and pediatric diseases.

However, few studies assessed RNFL thickness in preterm infants, so its clinical value in this cohort is unclear. We previously conducted a pilot study to assess RNFL thickness in very preterm infants utilizing handheld OCT systems.[17] We found that thinner RNFL at term equivalent age was associated with lower scores of cognitive and motor functions at 18–24 months corrected age, suggesting RNFL thickness may reflect the brain as a whole in infants.[17] To further investigate the retinal microanatomy in preterm infants, we initiated a prospective observational STudy of Eye imaging in Preterm infantS (BabySTEPS; ClinicalTrials.gov: NCT02887157).[18 19] Our recent data from BabySTEPS demonstrated that birth weight independently predicted RNFL thickness at 36 weeks postmenstrual

age (PMA) in preterm infants, suggesting that intrauterine processes may affect RNFL thickness.[18] However, it remains unknown if systemic diseases occurring during the NICU stay, which have been associated with increased risk of neurodevelopmental impairment, affect RNFL thickness in preterm infants. This study investigated the associations between systemic factors and RNFL thickness in preterm infants at 36 weeks PMA before any treatment for retinopathy of prematurity (ROP).

METHODS

Study Participants and Procedure

We previously described the BabySTEPS design in separate papers.[18 19] Briefly, BabySTEPS is a prospective observational study to investigate the relationship between retinal microanatomy and vision, neurodevelopment, systemic development, and ROP in preterm infants. Enrolled infants were eligible for ROP screening based on the American Association of Pediatrics guidelines.[20] The parent or legal guardian provided informed consent to participate in the study. Enrollment extended from August 2016 through November 2019 at Duke University Health System. Infants were excluded if they (1) were unable to receive an eye examination or imaging due to a health or eye condition, or (2) had a health condition (e.g., anencephaly, leukodystrophy) other than prematurity that had a profound impact on brain development. The Duke University Health System Institutional Review Board approved the study. The study adhered to the tenets of the Declaration of Helsinki, Good Clinical Practice, and the Health Insurance Portability and Accountability Act.

In the present analysis, we included infants with sufficient OCT imaging to measure RNFL thickness per protocol within 36 ± 1 weeks PMA before any ROP treatment.[18] We did not exclude eyes that received ROP treatment after OCT imaging at 36 ± 1 weeks PMA. Further details of inclusion, exclusion, OCT image capture, processing, and thickness measurements were reported in our previous paper.[18] Briefly, we used an investigational handheld high-speed, swept-source OCT system to image the infants' retina without sedation in the Duke intensive care nursery or Duke Regional Hospital nursery (Figure 1). The OCT system used near-infrared light, nearly invisible to infants; the imaging probe did not touch the infants' eyes. We used proprietary software to semi-automatically segment the OCT images and extract RNFL thickness in the papillomacular bundle.[17 18] We previously demonstrated excellent intra-grader and inter-grader reproducibility of RNFL thickness.[18] We included more detailed study design and RNFL thickness reproducibility results in online supplementary methods 1.

We extracted infant medical data from the medical record consistent with data collected for the Generic Database, a registry of clinical information of very low birth weight infants born alive in Eunice Kennedy Shriver NICHD Neonatal Research Network centers (ClinicalTrials.gov: NCT00063063). Intracranial hemorrhage (ICH), periventricular leukomalacia (PVL), and ventriculomegaly (VM) were diagnosed based on standard care cranial ultrasound. Sepsis was defined as positive blood culture, including both early-onset (≤72 hours after birth) or late-onset (>72 hours after birth) septicemia. NEC was defined as Bell's stage II or higher.[21] Birth weight percentile was calculated based on Fenton Preterm

Growth Chart.[22] Infant's growth velocity was calculated as $(W_2 - W_1)/[(W_2 + W_1)/2]/1000/$ number of days, where W_2 is infant's weight at the time of OCT imaging and W_1 is infant's weight on day 7 of life.[23] The definitions of other systemic diseases are in online supplementary methods 2.

Statistical Analysis

We performed statistical analysis using R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were reported in mean ± standard deviation unless otherwise specified. Since we previously found a strong correlation of RNFL thickness between the right and left eyes in this cohort (r = 0.80),[18] we used the mean RNFL thickness of both eyes of an infant when the data were available.

We performed univariable regression of RNFL thickness with 29 systemic health factors selected based on literature. These factors are listed in the results tables. Systemic factors with <10 infants in a subgroup of a factor were excluded from our analysis. We did not include the ROP stage and plus disease in the present analysis because our previous study in this cohort showed that neither condition was associated with RNFL thickness at 36 weeks PMA after adjustment for birth weight.[18] The association between RNFL thickness and brain magnetic resonance imaging findings will be reported separately.

To identify independent factors associated with RNFL thickness, we performed a multivariable analysis with a forward selection procedure (using "mixlm" package in R) based on *P* values (< 0.05 asthe selection criterion). In this selection process, we considered only variables significantly ($P < 0.05$) associated with RNFL thickness in the univariable model.

RESULTS

Study Cohort

We included 83 infants (159 eyes) in the present study. The birth weight was 974.4 ± 272.2 grams, and the gestational age was 28.0 ± 2.5 weeks. Sixteen out of 83 infants had sepsis/NEC. The onset of sepsis/NEC occurred before OCT imaging in all 16 infants, and the time from the onset of sepsis/NEC to OCT imaging was 50 ± 22 days. Other characteristics of the cohort are in Table 1.

Univariable Association Between Systemic Factors and RNFL Thickness

RNFL thickness was not associated with any 9 maternal factors in this cohort ($P > 0.05$; online supplementary Table 1). RNFL thickness was comparable between infants whose mothers smoked and whose mothers did not smoke during pregnancy (62.0 ± 12.2 vs. 60.9 ± 10.4 μm, $P = 0.70$).

Gestational age,[18] birth weight,[18] weight at OCT imaging (r = 0.57; $P < 0.001$), growth velocity (r = 0.37; $P < 0.001$), birth head circumference (r = 0.42; $P < 0.001$), or birth body length (r = 0.40; $P < 0.001$) was associated with RNFL thickness (Table 2). By contrast, infant sex, Apgar score at 1 minute or Apgar score at 5 minutes was not associated with RNFL thickness ($P > 0.05$; online supplementary Table 2).

RNFL was thinner in infants with more days of supplemental oxygen by 36 weeks PMA (r = −0.31; $P = 0.005$), respiratory support at 36 weeks PMA (−6.1 μm, 95% confidence interval (CI) = −11.7 to −0.5), pulmonary interstitial emphysema (−6.4 μm, 95% CI = −12.5 to −0.2), treated PDA (−5.2 μm, 95% CI = −10.3 to −0.2), sepsis/NEC (−10.4 μm, 95% CI = −15.9 to −4.9), or transfusion of packed red blood cells (−6.4 μm, 95% CI = −11.7 to −1.2) (Table 2). In contrast, surfactant administration, bronchopulmonary dysplasia, PDA, abnormal brain cranial findings (ICH, PVL, or VM), or erythropoiesis-stimulating agent administration was not correlated with RNFL thickness ($P > 0.05$; online supplementary Table 2).

Multivariable Association Between Systemic Factors and RNFL Thickness

Twelve factors were significantly associated with RNFL thickness based on the univariable model (Table 2). By including these factors in a multivariable model with a forward selection procedure, we found that infant weight at OCT imaging and sepsis/NEC were independently associated with RNFL thickness. In this multivariable model (Table 3), a 250-gram increase in infant weight at OCT imaging was associated with 2.7 μm (95% CI = 1.7 to 3.8; $P < 0.001$) increase in RNFL thickness, and sepsis/NEC was associated with −5.6 μm (95% CI = −10.8 to −0.3; $P = 0.04$) change in RNFL thickness. RNFL thickness difference between infants with versus without sepsis/NEC remained statistically significant and of comparable magnitude after adjustment for different confounding variables: (1) birth weight and gestational age (−7.4 μm, 95% CI = −12.8 to −1.9; $P = 0.008$; online supplementary Table 3), (2) birth weight percentile and gestational age (−7.3 μm, 95% CI = −13.0 to −1.7; $P = 0.01$; online supplementary Table 4), or (3) growth velocity and gestational age (−8.3 μm, 95% CI = −14.2 to −2.4; $P = 0.006$; online supplementary Table 5).

Based on the univariable model, RNFL was 10.4 μm thinner overall in infants with versus without sepsis/NEC (52.7 ± 9.0 vs. 63.1 ± 10.2 μm; $P < 0.001$; Table 2). RNFL thickness difference in infants with versus without sepsis/NEC was comparable for both right and left eyes: RNFL was 10.0 μm thinner in right eyes (54.9 ± 8.9 vs. 64.9 ± 11.4 μm; $P = 0.002$), and 9.6 μm thinner in left eyes (51.7 ± 9.7 vs. 61.3 ± 10.1 μm; $P = 0.001$) (Figure 2). The inter-eye difference in RNFL thickness (right minus left eyes) was comparable between infants with and without sepsis/NEC (2.7 ± 6.1 vs. 3.5 ± 7.4 μm; $P = 0.73$). The gestational age and birth weight were 25.8 ± 1.8 weeks and 769.7 ± 224.2 grams in infants with sepsis/NEC and were 28.5 ± 2.4 weeks and 1023.3 ± 260.9 grams in infants without sepsis/NEC.

A 250-gram increase in infant weight at OCT imaging was associated with 3.1 μm (95% CI = 2.1 to 4.2) increase in RNFL thickness based on univariable analysis ($P < 0.001$; Table 2). Our previously reported association between birth weight and RNFL thickness[18] remained statistically significant after adjustment for gestational age and sepsis/NEC ($P < 0.001$; online supplementary Table 3).

DISCUSSION

In this prospective observational study, we investigated the associations between systemic factors and RNFL thickness in 83 preterm infants at 36 weeks PMA. Among 29 systemic factors investigated in the study, 12 factors were significantly associated with RNFL

thickness in the univariable model. The multivariable analysis showed that low infant weight at OCT imaging and sepsis/NEC were independently associated with thinner RNFL. These findings, together with our recently reported association between birth weight and RNFL thickness[18] suggest that poor intrauterine and postnatal growth, as well as sepsis/NEC, may adversely affect optic nerve development in preterm infants, corresponding with previous reports of impaired long-term neurodevelopment in these infants.[3 4] To our knowledge, this study is the first to demonstrate a significant association between sepsis/NEC and RNFL thickness in preterm infants while in the NICU, suggesting that OCT-measured RNFL thickness may offer a potential noninvasive biomarker to assess the negative impact of sepsis/NEC on the central nervous system in preterm infants during their critical postnatal weeks before reaching term equivalent age. A future prospective study with a large cohort is required to validate these findings.

Our previous pilot study of 57 infants using an older OCT imaging system suggested a trend towards thinner RNFL in preterm infants with sepsis or NEC, although without statistical significance likely due to lower statistical power: median RNFL thickness was 9 μm lower in infants with versus without culture-positive sepsis ($P = 0.10$).[17] Compared with the present study (83 infants imaged at 36 ± 1 weeks PMA), our prior study had a smaller number of preterm infants (57 infants) and a wider OCT imaging window (37–42 weeks PMA). The latter may have contributed to the larger standard deviation of RNFL thickness than in the present study (17 vs. 10.7 μm). These limitations in that first study's design may explain why we previously did not detect a statistically significant difference in RNFL thickness between infants with and without sepsis or NEC.[17]

Two possible mechanisms exist to explain the thinner RNFL in infants with sepsis/NEC. Since both neonatal sepsis and NEC are associated with overwhelming systemic inflammation,[24] systemic inflammatory mediators may disrupt the blood-retinal barrier and damage retinal ganglion cells or axons. This hypothesis is supported by animal studies that demonstrated these inflammatory mediators' abilities to disrupt the blood-retinal barrier[25] and promote retinal ganglion cells degeneration.[26] Moreover, Pacheco-Cervera et al found a higher systemic level of interleukin-6 was associated with thinner RNFL in obese children.[16] Dias-Santos et al reported that adults with systemic lupus erythematosus without ophthalmologic manifestations had significantly thinner RNFL than healthy controls.[13] These clinical studies further suggest a link between systemic inflammation and RNFL thickness.

Another possible explanation for the association between sepsis/NEC and RNFL thickness is that sepsis/NEC may damage brain regions covering the visual track (via ischemia, infection, or inflammation), which may, in turn, cause retrograde trans-synaptic degeneration of retinal ganglion cells, resulting in thinner RNFL. Trans-synaptic retrograde degeneration has been proposed to play a role in RNFL thinning in patients with occipital lobe ganglioglioma, Alzheimer's disease, multiple sclerosis, and Parkinson's disease.[27 28] Alternatively, the same vulnerability to sepsis/NEC may in parallel make the same infant susceptible to brain injury. These hypotheses are consistent with brain magnetic resonance imaging findings of significant white matter abnormalities in infants with sepsis or NEC.[2] We did not find an association between ultrasound findings of brain abnormalities (ICH,

PVL, or VM) and RNFL thickness in this cohort (supplementary table 2). In a separate study with some overlapping infants, we are analyzing the relationship between OCT findings and research MRI findings. Since sepsis/NEC's impact on RNFL thickness was comparable in both right and left eyes, future studies may only need to image the right or left eyes instead of both eyes to evaluate the impact of sepsis/NEC on RNFL thickness in preterm infants.

Very preterm infants are vulnerable to early-life stressors including physiological, environmental, and experimental stressors. Traditional ROP exam using binocular indirect ophthalmoscopy (BIO) is a repeated experimental stressor to infants.[29] Therefore, one of the aims of the BabySTEPS is to identify a less stressful imaging method to evaluate ROP in these infants. We previously showed that ROP exam by OCT imaging is significantly less stressful than BIO examination by a trained ophthalmologist based on infant cry score, facial expression, and heart rate.[29] Given the limited OCT data in very preterm infants, future studies are still required to evaluate clinical relevance of adding or substituting OCT imaging in this vulnerable cohort.

Previous studies in school-age children reported inconsistent results on the relationship between gestational age and RNFL thickness. Some studies found thinner RNFL in children born with lower gestational age,[30 31] while other studies showed that gestational age was not significantly associated with RNFL thickness after adjustment for birth weight.[32 33] In our cohort, gestational age was positively associated with RNFL thickness at 36 weeks PMA based on univariable analysis (1.3 μm/week, $P < 0.001$). However, the association was not statistically significant after adjustment for birth weight (−0.8 μm, $P = 0.19$), and became negative after adjustment for birth weight and sepsis/NEC (−1.2 μm, $P = 0.048$). The unstable results may be due to relatively high collinearity between the 3 variables and the small sample size. Notably, the magnitude of the association between gestational age and RNFL thickness was small (approximately 1 μm per week), suggesting the impact of gestational age on RNFL thickness is not clinically important. Additionally, the Apgar score is an indicator of the health status and response to resuscitation immediately after the birth of a newborn. We did not find a significant association between RNFL thickness and Apgar score at 1 minute and 5 minutes (online supplementary table 2), suggesting that the transient health status at birth may not have a large impact on RNFL thickness at 36 weeks PMA. However, the relatively small number of infants in the study may limit the statistical power in finding a small but statistically significant association between RNFL thickness and Apgar score.

Two previous studies showed a significant association between maternal smoking during pregnancy and thinner RNFL in school-age children.[34 35] The authors suggested that intrauterine exposure to tobacco smoke could interfere with optic nerve development. However, since both studies measured RNFL thickness in children around 10 years old, the previous findings could be confounded by passive exposure to tobacco smoke after birth.[34 35] By directly measuring RNFL thickness in preterm infants at 36 weeks PMA, we examined the association between maternal smoking and RNFL thickness with less confounding effects from events after birth. To our surprise, RNFL thickness was comparable between infants whose mothers reported smoking and whose mothers did not report smoking during pregnancy (62.0 ± 12.2 vs. 60.9 ± 10.4 μm; $P = 0.70$). Given the

small number of infants with maternal smoking history (18 infants) and the existence of multiple comorbidities in preterm infants, we cannot conclude that intrauterine exposure to tobacco smoke does not affect optic nerve development. Also, maternal smoking may affect later optic nerve development after birth, which was not assessed in our study.

Our study has several limitations. First, although we prospectively designed the BabySTEPS to investigate the associations between systemic factors and RNFL thickness, we did not design our study to specifically evaluate the impact of sepsis/NEC on RNFL thickness. Therefore, a future prospective study is required to enroll a large cohort of infants with sepsis/NEC and a group of matched infants without sepsis/NEC to validate our findings. A future study should also investigate whether RNFL thickness is affected by the severity and treatment of sepsis/NEC in these infants. Second, our study has a relatively small sample size, which may preclude us from identifying other systemic factors associated with RNFL thickness in preterm infants. For example, 7 infants in our cohort had intraventricular hemorrhage diagnosed by standard care ultrasound. Since the number was less than 10, we did not include intraventricular hemorrhage in our analysis per protocol. Third, we do not yet have long-term neurodevelopmental outcomes on these infants, although that is planned. Fourth, many preterm infants had multiple systemic conditions. For example, among the 16 infants with sepsis/NEC, all of them received packed red blood cell transfusions, and 6 of them had treated PDA (online supplementary Table 6). Due to the relatively small sample size in this study, we were unable to perform a subgroup analysis to investigate the effects of different combinations of systemic factors on RNFL thickness.

CONCLUSIONS

In our study, low infant weight and sepsis/NEC were independently associated with thinner RNFL in preterm infants at 36 weeks PMA. To our knowledge, the present study is the first to suggest that sepsis/NEC may adversely affect retinal neurodevelopment. OCT-measured RNFL thickness may offer a noninvasive biomarker to assess the negative impact of sepsis/NEC on the central nervous system in preterm infants. Future prospective studies with large cohorts are required to validate our findings and investigate whether RNFL thickness can help clinicians or researchers monitor neurodevelopment, determine eligibility for clinical trials, or evaluate neuroprotective treatment response in preterm infants with sepsis/NEC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

Our prospective observational study of 83 preterm infants suggested that low infant weight and sepsis/necrotizing enterocolitis were independently associated with thinner retinal nerve fiber layer at 36 weeks postmenstrual age.

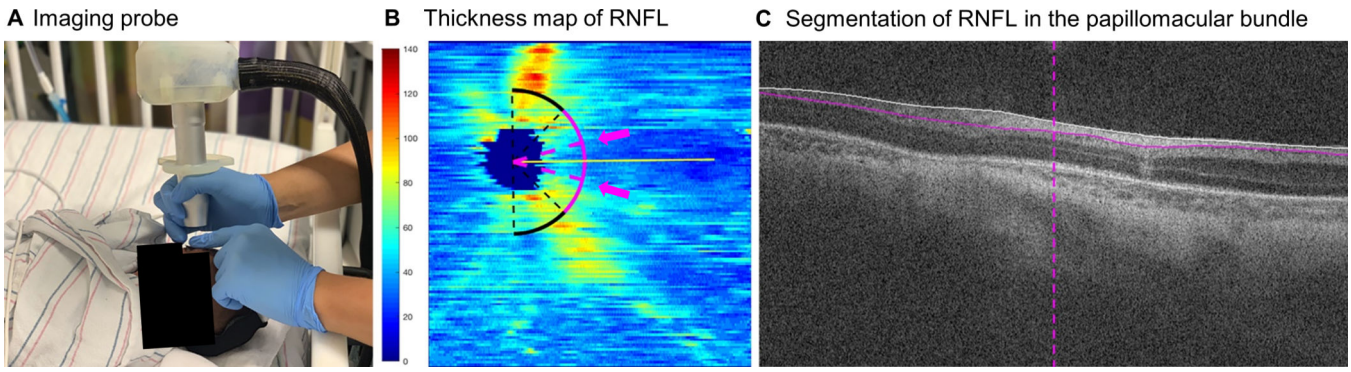

Figure 1.

Optical coherence tomography (OCT) imaging system and segmentation of retinal nerve fibre layer (RNFL). (A) The ultracompact, non-contact, hand-held imaging probe imaged a preterm infant at the bedside. (B) RNFL thickness map (in μm) of an eye from a preterm infant with late-onset sepsis in our cohort. The yellow solid line indicates the organising axis from the optic nerve centre to the fovea. The pink arc between two dashed pink lines and arrows represents the papillomacular bundle (arc from −15 to +15° relative to the organising axis). (C) Segmentation of RNFL (between the white and pink solid lines) in the papillomacular bundle (vertical dashed pink line) in an OCT b-scan of the same eye shown in B.

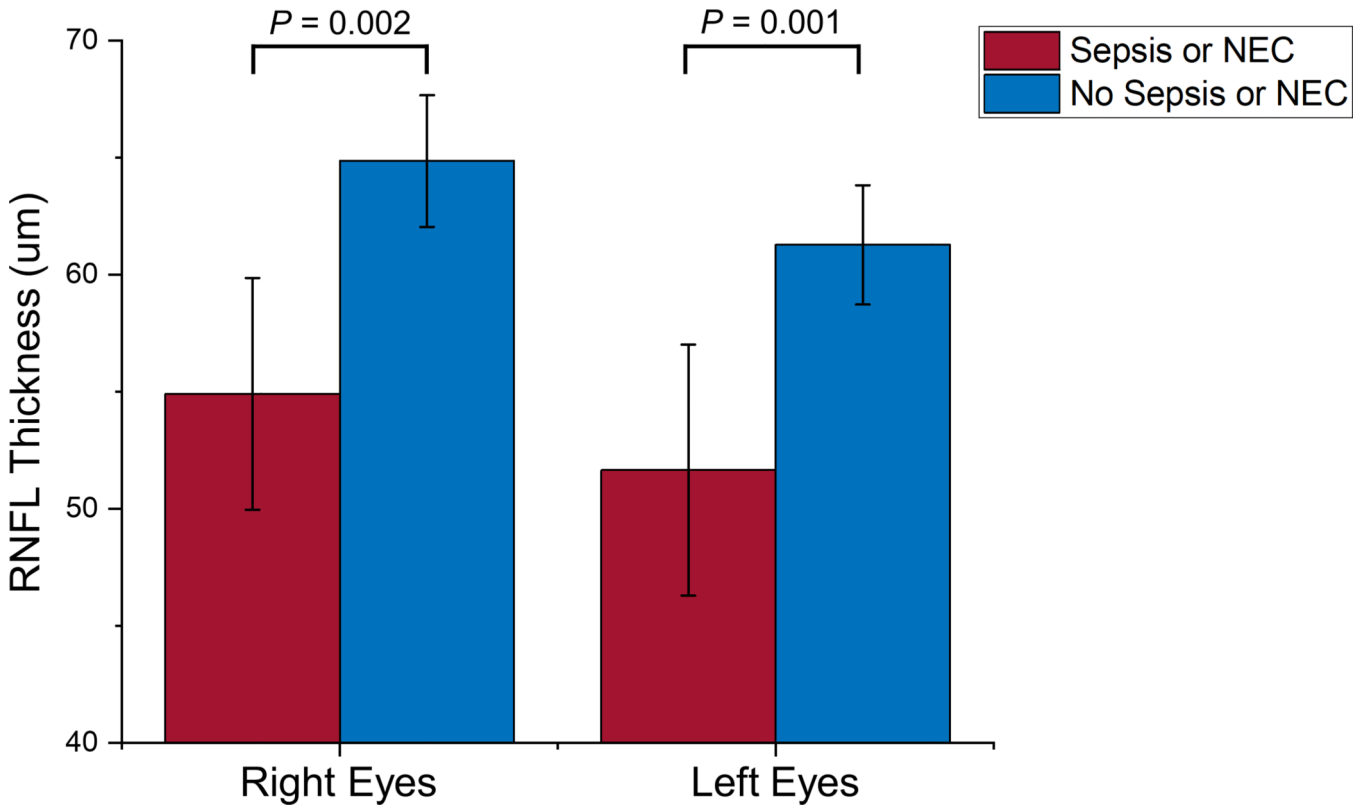

Figure 2.

Comparison of retinal nerve fibre layer (RNFL) thickness between preterm infants with and without sepsis or necrotising enterocolitis (NEC). The error bar represents the 95% CI. RNFL in the right eyes was 10.0 μm thinner in infants with sepsis/NEC (54.9±8.9 μm; N=15 eyes) than in infants without sepsis/NEC (64.9±11.4 μm; N=66 eyes) (p=0.002). Similarly, RNFL in the left eyes was 9.6 μm thinner in infants with sepsis/NEC (51.7±9.7 μm; N=15 eyes) than in infants without sepsis/NEC (61.3±10.1 μm; N=63 eyes) (p=0.001). The intereye difference in RNFL thickness (right–left eyes) was comparable between infants with and without sepsis/NEC (2.7±6.1 μm vs 3.5±7.4 μm; p=0.73).

Table 1.

Characteristics of the Study Cohort

Number of infants	83
Sex, n (%)	
Male	41 (49.4)
Race, n (%)	
African-American	37 (44.6)
Asian	5 (6.0)
White	38 (45.8)
More than one	3 (3.6)
Ethnicity, n (%)	
Non-Hispanic	76 (91.6)
Maternal age at delivery, mean (SD), y	30.2 (6.1)
Gestational age, mean (SD), wks	28.0 (2.5)
PMA at OCT imaging, mean (SD), wks	36.1 (0.6)
Birth weight, mean (SD), gm	974.4 (272.2)
Weight at OCT imaging, mean (SD), gm[a]	1601.1 (487.4)
Growth velocity, mean (SD), gm/kg/d[b]	12.6 (4.2)
Birth head circumference, mean (SD), cm	24.6 (2.36)
Birth body length, mean (SD), cm	34.9 (3.9)
Apgar score at 1 minute, mean (SD)	4.6 (2.5)
Apgar score at 5 minute, mean (SD)	6.7 (2.1)
Days on supplemental oxygen by 36 wks PMA, mean (SD)	14.4 (21.7)
RNFL thickness, mean (SD),μm	61.1 (10.7)

OCT, optical coherence tomography; PMA, postmenstrual age; RNFL, retinal nerve fiber layer; SD, standard deviation.

[a]Absent for 1 infant.

[b]Growth velocity was calculated using the average 2 – point method: $(W_2 - W_1) / [(W_2 + W_1)/2] /1000 /$ number of days, where W_2 is infant weight at the time of OCT imaging and W_1 is infant weight on day 7 of life. Growth velocity was missing for 2 infants: one did not have weight at day 7 and the other at the time of OCT imaging.

Table 2.

Univariable Analysis for Factors Associated with Retinal Nerve Fiber Layer Thickness

	Infant number	Coefficient estimate (μm)	95% Confidence interval (μm)	*P* value
Demographics and Birth Factors				
Gestational age, wk	83	1.3	(0.4, 2.2)	0.007
Birth weight, per 250 gm increase	83	5.2	(3.3, 7.0)	< 0.001
Weight at OCT imaging, per 250 gm increase[a]	82	3.1	(2.1, 4.2)	< 0.001
Growth velocity, gm/kg/d[b]	81	0.9	(0.4, 1.4)	< 0.001
Birth head circumference, cm	83	1.9	(1.0, 2.8)	< 0.001
Birth body length, cm	83	1.1	(0.5, 1.7)	< 0.001
Pulmonology				
Days on supplemental oxygen by 36wks PMA	83	−0.2	(−0.3. −0.1)	0.005
Respiratory support at 36 wk				
PMA				
Yes[c]	18	−6.1	(−11.7, −0.5)	0.03
No	65	Reference	- -	-
PIE				
Yes	14	−6.4	(−12.5, −0.2)	0.04
No	69	Reference	- -	-
Cardiology				
Treated patent ductus arteriosus				
Yes	24	−5.2	(−10.3, −0.2)	0.04
No[d]	59	Reference	- -	-
Systemic Hyperinflammatory Response				
Sepsis/NEC				
Yes[e]	16	−10.4	(−15.9, −4.9)	< 0.001
No	67	Reference	- -	-
Hematology				
PRBC transfusion				
Yes	62	−6.4	(−11.7, −1.2)	0.02
No	21	Reference	- -	-

NEC, necrotizing enterocolitis; OCT, optical coherence tomography; PMA, postmenstrual age; PRBC, packed red blood cells; PIE, Pulmonary interstitial emphysema.

[a]Weight at the time of OCT imaging was lacking for 1 infant.

[b] Growth velocity was calculated using the average 2-point method: (W2 –W1) / [(W2 + W1)/2] /1000 / number of days, where W_2 is infant's weight at the time of OCT imaging and W_1 is infant's weight on day 7 of life. Growth velocity was missing for 2 infants: one did not have weight at day 7 and the other at the time of OCT imaging.

[c] Respiratory support included : continuous positive airway pressure therapy in 2 infants, conventional ventilation in 3 infants, nasal ventilation in 1 infant, and oxygen by nasal cannula in 12 infants.

[d] Among 59 infantswithout treated PDA, 46 infants did not have PDA and 13 had PDA but did not receive treatmentby 36 weeks PMA.

[e] 12 infants had culture positive sepsis (11 late-onset septicemia and 1 early-onset septicemia) and 5 infants had NEC (3 surgical NEC and 2 medical NEC). Among them, 1 infant had both sepsis and NEC.

Table 3.

Multivariable Analysis for Factors Associated with Retinal Nerve Fiber Layer Thickness

	Coefficient estimate (μm)	95% Confidence interval (μm)	*P* value
Weight at OCT imaging, per 250 gm increase	2.7	(1.7, 3.8)	< 0.001
Sepsis/NEC, yes	−5.6	(−10.8, −0.3)	0.04

NEC, necrotizing enterocolitis