Evaluation of Optic Nerve Development in Preterm and Term Infants Using Handheld Spectral-Domain Optical Coherence Tomography

Amy Y. Tong, BS,[1] Mays El-Dairi, MD,[1,2] Ramiro S. Maldonado, MD,[1] Adam L. Rothman, BS,[1] Eric L. Yuan, BS,[1] Sandra S. Stinnett, DrPH,[1] Laura Kupper, MD,[2] C. Michael Cotten, MD,[2] Kathryn E. Gustafson, PhD,[2] Ricki F. Goldstein, MD,[2] Sharon F. Freedman, MD,[1,2] Cynthia A. Toth, MD[1,3]

Purpose: To evaluate effects of prematurity on early optic nerve (ON) development and the usefulness of ON parameters as indicators of central nervous system (CNS) development and pathology.

Design: Prospective, cross-sectional, longitudinal study.

Participants: Forty-four preterm infants undergoing retinopathy of prematurity (ROP) screening and 52 term infants.

Methods: We analyzed ON from portable handheld spectral-domain optical coherence tomography (SD-OCT) images (Bioptigen, Inc, Research Triangle Park, NC) of 44 preterm and 52 term infants. The highest-quality ON scan from either eye was selected for quantitative analysis. Longitudinal analysis was performed at 31−36 weeks and 37−42 weeks postmenstrual age (PMA). Preterm ON parameters also were assessed for correlation with indicators of cognitive, language, and motor development and CNS pathology.

Main Outcome Measures: Vertical cup diameter (vCD), vertical disc diameter (vDD), vertical cup-to-disc ratio (vCDR), cup depth, and indicators of neurocognitive development and CNS pathology.

Results: At 37−42 weeks PMA, preterm infants had larger vCD and vCDR than term infants (908 vs. 700 μm [$P<0.001$] and 0.68 vs. 0.53 μm [$P<0.001$], respectively), whereas cup depth and vDD were not significantly different. Longitudinal changes (n = 26 preterm eyes; mean interval, 4.7 weeks) in vDD and in vCDR were an increase of 74 μm ($P = 0.008$) and decrease of 0.05 ($P = 0.015$), respectively. In preterm infants (n = 44), periventricular leukomalacia was associated with larger vCD (1084 vs. 828 μm; $P = 0.005$) and vCDR (0.85 vs. 0.63; $P<0.001$), posthemorrhagic hydrocephalus was associated with shallower cup (331 vs. 456 μm; $P = 0.030$), and clinical magnetic resonance imaging was associated with larger vCDR (0.73 vs. 0.64; $P = 0.023$). In 23 preterm infants with Bayley Scales of Infant Development scores, larger vCDR was associated with lower cognitive scores ($P = 0.049$).

Conclusions: This is the first analysis of ON parameters in premature infants using SD-OCT. It demonstrated that by age of term birth, vCD and vCDR are larger in preterm infants who were screened for ROP than in term infants. In this prospective pilot study, ON parameters in these preterm infants associate weakly with CNS pathology and future cognitive development. Future prospective studies with larger numbers are necessary before further conclusions can be made. *Ophthalmology 2014;■:1−9 © 2014 by the American Academy of Ophthalmology.*

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To date, our understanding of perinatal optic nerve (ON) development comes from histopathologic studies, which have shown that the in utero ON axonal count peaks at approximately 16 to 17 weeks gestational age and decreases until approximately 32 weeks.[1] Additional histopathologic studies have shown that the optic disc and retrobulbar nerve reach 75% of adult size by term birth,[2] that both correlate with globe anteroposterior diameter,[2] and that the retrobulbar nerve grows during infancy as a result of myelination.[2,3]

Imaging technologies such as digital fundus photography and optical coherence tomography (OCT) have allowed for in vivo studies of the living optic nerve. Optical coherence tomography studies in school-aged children suggest that history of and characteristics common to prematurity are associated with decreased optic neuronal tissue.[4−6] Other studies have found racial variation, with black children having larger cup-to-disc ratios and thicker retinal nerve fiber layers (RNFLs).[7] Additionally, both adult and pediatric studies have shown intracranial pathologic features to be associated with thinner RNFL.[8−10] The only study comparing infant ON parameters with measurements associated with birth status has been a Retcam (Clarity Medical Systems, Inc, Pleasanton, CA) study assessing the effect of

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low birth weight in term infants.[11] To date, we are not aware of OCT studies that address how prematurity affects ON development during infancy (PubMed MeSH terms *infant* AND *optical coherence tomography* AND *optic nerve*). In the present study, we used spectral-domain (SD-) OCT to explore whether differences exist during infancy between preterm and term infant ON measurements and to assess the relationship between these parameters and indicators of central nervous system (CNS) pathologic features.

Methods

This Health Insurance Portability and Accountability Act–compliant prospective study was approved by the Duke University Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. From April 2009 through October 2012, SD-OCT images were obtained from 90 preterm infants at the Duke Neonatal Intensive Care Unit (NICU) and from 60 term infants in the Duke Birthing Center. Preterm infants were eligible if undergoing retinopathy of prematurity (ROP) screening, which required either birth at 30 weeks gestational age or earlier or a birth weight of 1500 g or less. Term infants born at 36 weeks gestational age or more and without known medical problems were eligible. Fifty-eight of these 60 term infants also were in a report by Allingham et al.[12]

Birth weight, gestational age, race and ethnicity, gender, and ROP status were recorded at the initial imaging session. Subjects were defined as Asian, black, Hispanic, and white. Similar to a study by Knight et al,[13] Hispanic was considered a racial group, although subjects of Hispanic ethnicity and black race were considered to be black.

Spectral-domain OCT volumes consisting of multiple vertical B-scans were captured with an 840-nm wavelength portable SD-OCT system (Bioptigen, Inc, Research Triangle Park, NC).[14] Scans with sufficient focus and alignment to allow identification of Bruch's membrane opening and the deepest point of the optic cup were eligible; based on a subjective assessment of focus, resolution, centering of the optic nerve, and lack of tilt, the highest-quality volume scan of the ON from 1 eye of each subject was selected for quantitative analysis. From the volume, B-scans with the largest vertical cup diameter (vCD), vertical disc diameter (vDD), and cup depth were selected and de-identified for analysis (up to 3 B-scans from the same volume if necessary). For the primary analysis of term versus preterm infants, subjects had at least 1 adequate scan from 37 to 42 weeks postmenstrual age (PMA). Analysis of longitudinal ON growth included eyes of 26 preterm infants from the primary analysis who also underwent imaging at 31 to 36 weeks PMA (selecting the earliest adequate imaging session if there were multiple).

For the analysis of ON parameters and markers of CNS pathologic features, we reviewed medical records of preterm infants in the primary study for Bayley Scales of Infant and Toddler Development, Third Edition, scores at 18 to 22 months corrected age; drop-off in head circumference growth from NICU discharge until follow-up at 18 to 22 months corrected age; receipt of magnetic resonance imaging (MRI); presence and grade of intraventricular hemorrhage on ultrasound; presence of periventricular leukomalacia (PVL) by ultrasound or MRI; head circumference at NICU admission and discharge; and 5-minute Apgar score. Bayley scores were chosen to measure CNS development because they are standardized, norm-referenced measures shown to have adequate reliability and validity and are considered the gold standard of infant and toddler development assessment tools.[15]

Quantitative analysis required a MATLAB script (MathWorks, Inc., Natick, MA), which allowed the masked grader (A.Y.T.) to mark the vDD, vCD, and cup depth (Fig 1). The vertical cup-to-disc ratio (vCDR) then was calculated. A senior masked grader (R.S.M.) and faculty (C.A.T.) audited all scans to confirm the markings. Vertical rather than horizontal ON parameters were measured because vertical scans were prioritized to image retinal vessels for assessment of plus disease in ROP[16] and because they are used more commonly in clinical assessments for glaucoma[17] and are less affected by nerve tilt. Lateral measurements within the scans were corrected using an age-based estimate of the infant eye's axial length.[14] To evaluate intergrader measurement reliability, 2 graders (A.Y.T. and A.L.R.) measured the same 10 randomly chosen masked scans. To evaluate interscan measurement reliability, 1 grader (A.Y.T.) measured 2 randomly chosen masked scans from 10 unique imaging sessions.

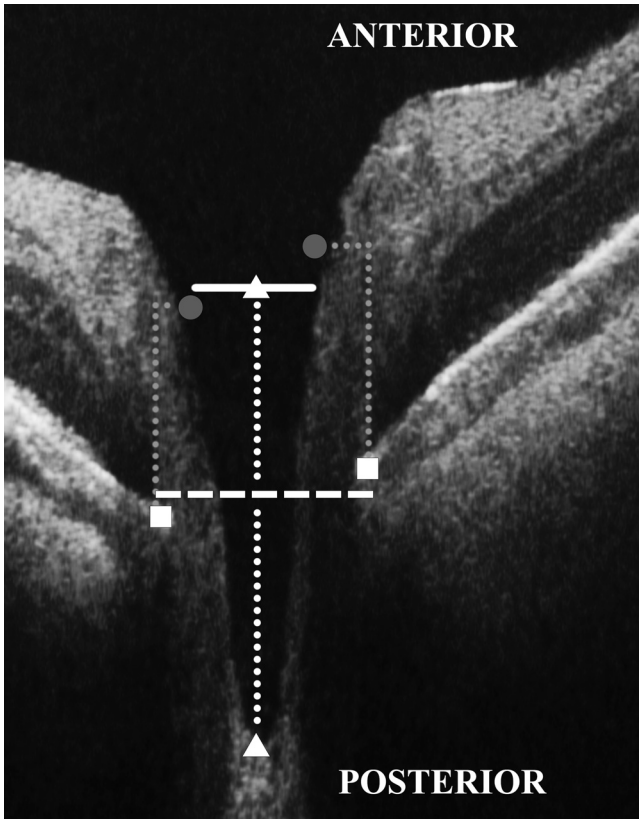

Figure 1. Measurement of optic nerve parameters in a spectral-domain optical coherence tomography (SD-OCT) scan of an infant optic nerve. Using cross-sectional SD-OCT B-scans, vertical disc diameter (vDD; dashed white line) and vertical cup diameter (vCD; solid white line) were measured parallel to the anterior and posterior surface of the scan (not on the diagonal), vertical cup-to-disc ratio (vCDR) was calculated, and cup depth (dotted white line) was measured parallel to the A-scans within the B-scan from the plane of the cup to the top of the lamina cribrosa (white triangles). To accommodate for image tilt in the B-scans, the plane of the disc (dashed white line) was defined as the plane halfway between the 2 points (white rectangles) defining Bruch's membrane opening, which can be visualized as the outer edge of the retinal pigment epithelium. The plane of the cup (solid white line) was defined as the plane halfway between the 2 points (gray circles) marking the cup border, set at a plane 200 μm superior to the Bruch's membrane opening markings; the same 200 μm offset was used in the Cirrus Optic Disc Cube protocol for SD-OCT.[13] To assess the effect a change in offset between cup and disc planes would have on our measurements, we conducted secondary analyses of the same scans using 150 μm instead of 200 μm as the offset.

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