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Macular Findings in Healthy Full-term Hispanic Newborns Observed by Hand-held Spectral-Domain Optical Coherence Tomography

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Abstract

BACKGROUND AND OBJECTIVE: To enhance understanding of ethnically diverse normal newborn retinal morphology, the authors report spectraldomain optical coherence tomography (SD-OCT) macular findings in healthy Hispanic newborns.

PATIENTS AND METHODS: In this IRB-approved prospective, observational case series, 20 full-term Hispanic newborns had dilated retinal examinations and imaging by hand-held SD-OCT without sedation at the Duke Birthing Center.

RESULTS: Of 20 newborns imaged (35% male; median gestational age: 39 weeks; range: 36 to 40 weeks), two (10%) had bilateral subfoveal fluid, including one case of bilateral double subretinal fluid pockets. Three eyes of two infants (10%) had retinal macular cystoid structures (one enlarged at 1.5 months, with resolution by 3 months). These SD-OCT findings were not visible by indirect ophthalmoscopy.

CONCLUSION: Some Hispanic newborns have subretinal fluid or macular cystoid structures on SD-OCT. This study expands our understanding of findings seen by SD-OCT in healthy full-term newborns of various races.

INTRODUCTION

A recent prospective, observational case series of primarily African American and Caucasian healthy newborn infants identified a number of cases of unsuspected foveal

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subretinal fluid and foveal cystoid structures by hand-held spectral-domain optical coherence tomography (SD-OCT).¹ Among 22 of 39 Caucasians (56%) and 15 of 39 African Americans (38%), five of the six infants (83%) with bilateral subretinal fluid were Caucasian, one of six (17%) was African American, and the one infant with cystoid macular changes was Caucasian.¹ It is not known whether these findings are also present in Hispanic newborns.

Racial differences in SD-OCT measurements of macular structure have been established in adults,² including Hispanics.³ Hispanic adults are thought to differ from other racial groups in the incidence of central serous retinopathy⁴ and age-related macular degeneration.⁵ Differences between African Americans and Caucasians in macular anatomy have been documented in the healthy pediatric population using optical coherence tomography, including differences in macular volume⁶ and foveal thickness.^{6–8} Pediatric SD-OCT imaging studies have not included Hispanics, however. The 2010 U.S. Census counts 50.5 million Hispanics living in the United States (16% of the population), up 15.2 million from 2000.⁹ With the introduction and expansion of hand-held SD-OCT imaging among infants and young children with ocular disease, the need for ethnicity-specific normative data in these populations is evident.

PATIENTS AND METHODS

Subjects

Twenty healthy full-term Hispanic infants were included in this prospective, observational study approved by the Duke University Health System institutional review board. The study is in compliance with the United States Health Insurance Portability and Accountability Act regulations. Infants were eligible for the study if they were born at 36 weeks of gestation or later and did not have known systemic disease. Eligible infants were identified and recruited in the Duke Birthing Center. Legal guardians of all infants enrolled in the study underwent informed consent in their primary language. Infants underwent dilated retinal examination by indirect ophthalmoscopy and retinal imaging by portable hand-held SD-OCT without sedation between January and May 2011. Infants' and mothers' medical records were reviewed for health history, delivery history, pregnancy history, gestational age of the infant at birth based on reconciliation of menstrual and ultrasound dating criteria, birth weight, and maternal age at the time of delivery.

Procedures

All infants had both eyes dilated by instillation of cyclopentolate 0.5% and phenylephrine 2.5%. Following pupillary dilation, a pediatric ophthalmologist (MTC) performed a clinical examination including indirect ophthalmoscopy with a 28-diopter lens and without an eyelid speculum.

The Envisu C2300 hand-held SD-OCT (Bioptigen, Research Triangle Park, NC) was used to image both eyes of all subjects following the age-customized method for SD-OCT in infants described by Maldonado et al,¹⁰ which allows imaging without sedation or a lid speculum. With this approach, multiple series of double-volumetric 800 A-scans × 80 B-scans centered

on the optic nerve or fovea, measuring approximately 7×7 mm, were captured. All infants were examined first with indirect ophthalmoscopy and then with SD-OCT to mask the clinician from the SD-OCT results. A study investigator later graded the images without knowledge of the indirect ophthalmoscopy results. The eyes of eight infants were identified to have abnormal findings either by SD-OCT or indirect ophthalmoscopy, and these subjects were asked to return for repeat examination in the clinic approximately 1 month later, including repeat SD-OCT imaging. Those infants with persistent pathology on either the dilated retinal examination or SD-OCT were then asked to return monthly until the abnormality resolved.

Image Processing

SD-OCT images were converted into Digital Imaging and Communications in Medicine (DICOM) format and qualitatively graded in OSIRIX medical imaging software (OSIRIX Foundation, Geneva, Switzerland) for the presence or absence of each retinal layer and for any pathologic abnormality present. Subretinal fluid was defined as an area of hyporeflectivity between the neurosensory retina and the retinal pigment epithelium. A cystoid space was defined as a distinctive area of hyporeflectivity within the neurosensory retina extending in three dimensions and causing associated distortion of retinal layers. The highest quality scan containing the fovea, based on a subjective assessment of resolution and volume, was selected for quantitative analysis for each imaging session from each eye.

To quantify retinal features, the retinal layers were semi-automatically segmented on a single central scan using the MATLAB-based (Mathworks, Natick, MA) software DOCTRAP¹¹ v10.2 (Duke University). A custom MATLAB script was implemented on the segmentation output to acquire measurements for retinal thickness and dimensions of retinal pathology.

The Mann-Whitney test was used to compare the foveal thickness measurements from the left eye of each infant. The Fisher exact test was used to compare rates of maternal diabetes mellitus between infants with and without subretinal fluid.

RESULTS

Twenty healthy Hispanic full-term (median: 39 weeks; range: 36 to 40 weeks) newborn infants (7 male; 35%) were recruited at the Duke Birthing Center between January and May 2011. All infants underwent examination and imaging within 48 hours after birth. Twelve infants were born via spontaneous vaginal delivery and eight were born via cesarean delivery. Eight infants were identified to have ocular pathology and were asked to return for follow-up 1 month later; however, only five of the eight returned and the others were lost to follow-up (Table).

Subretinal fluid

No cases of subretinal fluid were detected by indirect ophthalmoscopy. Four eyes of two of 20 infants (10%) had subfoveal fluid on SD-OCT. Infant No. 16 was delivered via cesarean and had a history of maternal thrombocytopenia. SD-OCT revealed bilateral single pockets of foveal subretinal fluid (Figure 1). Infant No. 3, born vaginally to a mother of advanced

maternal age, had bilateral double pockets of subretinal fluid in the foveal region, which resolved 2.5 months later (Figure 2). Subretinal fluid was hyporeflective with overlying hyperreflective outer retina in both cases (Table). Among all healthy full-term infants from the current and prior study¹ combined, two of eight (25%) with bilateral subretinal fluid had a history of maternal diabetes mellitus compared to two of 51 (4%) without subretinal fluid ($P = .08$).

Cystoid macular edema

No cases of macular cystoid structures were detected by indirect ophthalmoscopy. Three eyes of two of 20 infants (10%) had retinal macular cystoid structures on SD-OCT. Infant No. 5 had a maternal history of hyperthyroidism and multiple retinal cystoid structures seen parafoveally in both eyes at birth by SD-OCT. Infant thyroid levels were borderline high at 1.5 months (TSH: 0.34; normal range: 0.34 to 5.66; free T4: 1.42; normal range: 0.52 to 1.21), at which time a florid increase in macular edema was seen by SD-OCT. Thyroid levels improved 1 week later (TSH: 0.82; free T4: 1.63), and by 3 months the macular SD-OCT appeared normal (Figure 3). Another infant (No. 8) with a maternal history of thrombocytopenia was also found to have retinal cystoid structures on SD-OCT at birth, but only in the left eye. Both infants with cystoid edema were born vaginally and had co-existing retinal hemorrhages (Table).

The median total central foveal thickness at birth (including subretinal fluid) for all 40 eyes of 20 Hispanic infants was 90 μm (range: 65 to 128 μm). The median central foveal thickness for 33 eyes of 17 infants with normal foveal appearance on SD-OCT was 84 μm (range: 65 to 103 μm). In comparison, the four eyes of two infants with subretinal fluid had a median total central foveal thickness of 112 μm (range: 97 to 126 μm ; $P = .01$), while the median total central foveal thickness of the three eyes of two infants with cystoid macular edema was 105 μm (range: 100 to 128 μm ; $P = .01$).

DISCUSSION

Full-term, healthy Hispanic newborns exhibited similar retinal macular findings by hand-held SD-OCT to newborns of other races imaged in a recent study.¹ Previously, 22 Caucasian (56.4%), 15 African American (38.5%), one Asian (2.6%), and one Hispanic (2.6%) infant were imaged by SD-OCT, with six of 39 infants (15%) demonstrating the unexpected finding of bilateral subfoveal fluid,¹ compared to two of 20 (10%) Hispanic infants in the present study. The previous study also identified one of 39 cases (2.5%) of bilateral cystoid macular changes,¹ compared to two of 20 (three eyes, 10%) in the present study.

The cause of bilateral subfoveal fluid in the eyes of healthy, full-term infants is unknown. As previously suggested,¹ this could represent a new variant of central serous retinopathy occurring in the newborn, who may be more susceptible to circulating cortisol or other unknown risk factors causing the less common central serous retinopathy of pregnant mothers.⁴ Nonetheless, no mothers in this study carried the diagnosis of central serous retinopathy. The bilateral subretinal fluid appearance in healthy, full-term newborns appears to be exceptionally symmetric between the eyes, both in size and morphology. This series

includes the first reported case of bilateral double pockets of subretinal fluid in this population (Figure 2). This symmetry supports a systemic etiology, as opposed to local ocular changes. It is unknown whether maternal thrombocytopenia contributed to another infant's bilateral single pockets of subretinal fluid (Figure 1). Among all healthy full-term infants with bilateral subretinal fluid from the current and prior study¹ combined, two of eight (25%) with bilateral subretinal fluid had a history of maternal diabetes mellitus compared to two of 51 (4%) without subretinal fluid, approaching statistical significance ($P = .08$). Larger studies are necessary to establish systemic factors in the infant or mother that may contribute to subretinal fluid development in newborns. Alternatively, subfoveal fluid may represent a normal variant of macular anatomy in healthy newborns. Interestingly, subfoveal fluid was not reported in a series of prematurely born infants who underwent SD-OCT concurrent with retinopathy of prematurity screening examinations.¹² We cannot rule out the possibility that subfoveal fluid could have occurred at birth in these infants and then resolved by the first SD-OCT imaging session, which took place 4 to 6 weeks later.

Parafoveal cystoid structures have been documented by SD-OCT imaging in 16% of prematurely born infants imaged at a single time point,¹³ 61% of prematurely born infants imaged at multiple time points,¹² and only 5.1% (three of 59) of full-term infants (including two Hispanics in the present study and one Caucasian infant previously reported¹). This series includes the first reported case of progressive bilateral cystoid macular edema in a full-term newborn (Figure 3). Including this study, only 12 of 59 full-term infants reported in the literature have received follow-up imaging;¹ therefore, it remains unclear whether additional full-term infants in these studies actually developed cystoid macular changes later, as in this case. Newborn macular cystoid changes appear unrelated to subretinal fluid because, to date, no cases have documented the two findings together.^{1,12,13} Both cases of cystoid changes in the present study had coexisting retinal hemorrhages, although this was not seen in the single case from the previous study of healthy full-term infants.¹ While all three cases of full-term healthy newborns¹ were born vaginally, 57% of prematurely born infants¹² with cystoid macular changes were delivered via cesarean (personal correspondence). These cystoid macular changes could represent a normal variant of infant foveal morphology, or rather result from systemic disease risk factors (eg, maternal hyperthyroidism and thrombocytopenia seen here or hemochromatosis¹⁴ and prematurity^{12,13} seen previously).

Overall, 19% (11 of 59) of healthy full-term infants of various racial backgrounds demonstrated macular subretinal fluid or cystoid changes.¹ The visual consequences of these macular findings are unknown. Because rates of strabismus and nonrefractive vision reduction in the general population are far lower,¹⁵ the possibility of these infants developing significant visual impairment as a result of these macular findings seems unlikely. All six full-term infants from the current and prior study¹ with macular findings on SD-OCT who underwent follow-up examination demonstrated resolution of macular pathology by 1 to 4 months of age; however, the sample size of these studies is inadequate to document the full range of resolution times that might be seen in a large population. Perhaps there are unusual cases of cystoid changes or subretinal fluid persisting beyond 4 months and contributing to the development of delayed visual maturation, infantile idiopathic nystagmus, or other uncommon unexplained abnormalities in visual behavior. Further

follow-up is needed to determine whether newborn macular cystoid structures or subretinal fluid leads to these or other visual consequences. This study contributes to the diversity of reported unsuspected retinal macular findings in healthy newborns documented by SD-OCT. Clinicians and researchers should be aware of these retinal findings when performing SD-OCT in full-term newborns, including Hispanics.

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Figure 1.

Subretinal fluid (arrow) seen in the left eye of a healthy full-term Hispanic newborn (No. 16 in Table) by SD-OCT. Subretinal fluid height was 42 μm and width was 569 μm . The median height and width of subretinal fluid was 45 μm (range: 39 to 53 μm) and 644 μm (range: 551 to 752 μm), respectively, for all four eyes with subfoveal fluid (two of 20 healthy full-term Hispanic infants). The median total central foveal thickness (including subretinal fluid) was 112 μm (range: 97–126 μm).

Figure 2. Double pockets of subretinal fluid in a healthy full-term Hispanic newborn infant (No. 3 in Table). Subretinal fluid at birth (closed arrows) in the right (A) and left (C) eyes resolved by 2.5 months (B, D; open arrows).

Figure 3.

Increase in cystoid macular edema, which later resolved, seen at follow-up visit in one full-term Hispanic newborn (No. 5 in Table) with borderline hyperthyroidism. Bilateral mild cystoid macular edema identified by SD-OCT at birth (arrows) in the right (A) and left (D) eye increased at 1.5 months (B, E) and then resolved at 3 months (C, F). Thyroid levels were borderline high at 1.5 months but improved soon after.

TABLE
Demographic Prenatal and Delivery History and Retinal Findings for Healthy Hispanic Full-term Newborn Subjects

No.	Demographics			Systemic Findings		Infant	Delivery	Retinal Findings		Follow-up of abnormal findings (months)
	Sex	PMA (wks)	Birth weight (g)	Maternal				Eye	Clinical exam	SD-OCT
1	M	39	3,505	anemia	none		V	R	normal	normal
								L	normal	normal
2	M	39	3,560	none	none		C	R	normal	normal
								L	normal	normal
3*	F	39	3,050	AMA	none		C	R	normal	double SRF**
								L	normal	double SRF**
4	F	38	3,405	none	none		V	R	normal	normal
								L	normal	normal
5*	F	38	2,705	hyperthyroid, AMA	borderline hyperthyroid		V	R	RH	CME
								L	RH	CME
6	F	39	3,115	AMA	none		C	R	normal	normal
								L	normal	normal
7	M	39	3,100	none	none		C	R	normal	normal
								L	normal	normal
8*	F	40	2,930	thrombocytopenia	none		V	R	RH	normal
								L	RH	CME
9	F	36	2,815	vitamin D deficiency	none		V	R	RH	normal
								L	RH	normal
10	F	40	2,475	pyelonephritis, anemia	none		V	R	normal	normal
								L	normal	normal
11	M	40	3,295	none	none		V	R	normal	normal
								L	normal	normal
12	F	39	4,270	AMA, gestational DM	none		V	R	RH	normal
										lost to follow-up

No.	Demographics		Systemic Findings		Infant	Delivery	Labor length (hr:min)	Retinal Findings		SD-OCT	Follow-up of abnormal findings (months)
	Sex	PMA (wks)	Birth weight (g)	Maternal				Eye	Clinical exam		
13	M	39	3,635	Bell's palsy	none	V	1:00	L	normal	normal	lost to follow-up
								R	RH	normal	resolved RH (1)
								L	RH	normal	resolved RH (1)
14	M	37	4,395	AMA, DM	oligohydramnios	C vacuum	0:00	R	normal	normal	no follow-up
								L	normal	normal	no follow-up
15*	F	40	3,510	none	none	V	3:52	R	normal	normal	normal (1)
								L	RH	ERM, preretinal tissue, resolved RH (1)	
16*	F	39	3,475	thrombocytopenia	none	C	0:00	R	normal	SRF	lost to follow-up
								L	normal	SRF	lost to follow-up
17	F	39	3,870	UTI	none	C	0:00	R	normal	normal	no follow-up
								L	normal	normal	no follow-up
18	F	39	3,315	anemia	none	V	0:10	R	normal	normal	no follow-up
								L	normal	normal	no follow-up
19	F	39	4,170	none	none	C	72:00	R	normal	normal	no follow-up
								L	normal	normal	no follow-up
20	M	39	3,715	obesity	cyanosis with feed	V	5:40	R	normal	normal	no follow-up
								L	normal	normal	no follow-up

PMA = postmenstrual age at birth based on reconciliation of menstrual and ultrasound dating criteria; Labor length = time from rupture of membranes to complete delivery; SD-OCT = spectral-domain optical coherence tomography; M = male; F = female; V = vaginal; C = cesarean; R = right eye; L = left eye; SRF = subretinal fluid; CME = cystoid macular edema; RH = retinal hemorrhages; ERM = epiretinal membrane; AMA = advanced maternal age (> 34 years); DM = diabetes mellitus; UTI = urinary tract infection.

* Macular pathology on SD-OCT.

** Two adjacent subretinal fluid pockets in the macula.

*** Follow-up for nonmacular pathology (optic nerve elevation).