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Morphological characteristics of early-versus late-onset macular edema in preterm infants

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Abstract

Macular images of infants with early-onset edema (occurring at or before 33 weeks' postmenstrual age [PMA]) and infants with late-onset edema (at or after 36 weeks' PMA) were compared. At first appearance, early-onset edema has a more severe morphology, with foveal bulging and elongated cystoid spaces than late-onset edema, which presents as small cystoid spaces outside the foveal center. Morphological variations may be an indicator of the underlying cause of edema in preterm infants. The presence of mostly parafoveal small cystoid spaces in the late-onset edema group may be suggestive of an association with neurological injury.

Ocular imaging and diagnosis in the vulnerable preterm infant population at risk for retinopathy of prematurity (ROP) is challenging. The advent of handheld spectral domain optical coherence tomography (SD-OCT) and its adaptation to infant use has enabled in vivo assessment of the infant retina and revealed macular edema (ME) at a very young age.^{1,2}

Macular edema has been found on SD-OCT in 30%–60% of preterm infants at risk for ROP.^{1,3} Studies to date have provided conflicting evidence regarding the relationship between ME and ROP⁴ and proposed associations with delayed photoreceptor development,⁵ neurodevelopmental delay,⁶ and decreased visual acuity.⁷ Together they highlight the possible monitoring of ME as a marker for the course of development of the eye and brain.^{6,7} In this study, we test our hypothesis that different morphological characteristics of ME in preterm infants is related to age at onset of edema, which may, in turn, correlate to systemic health factors.

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Subjects and Methods

The macular images from 185 preterm infants prospectively enrolled in a retinal imaging study (January 2010 to May 2017) of the portable handheld SD-OCT system Envisu (Leica Microsystems, IL) were reviewed retrospectively. This study was approved by the Duke University Health System Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Written informed consent of a parent or legal guardian was obtained prior to the original research activity. Eyes were included for analysis if there were at least two consecutive imaging sessions that captured the macula, if the first appearance of ME on OCT imaging could be documented, and if the subjects fit the early-onset or the late-onset group assignment.

To avoid overlap of study cohorts, early-onset edema was defined as onset at or before postmenstrual age (PMA) of 33 weeks and 0 days; late-onset edema, as at or after 36 weeks and 0 days.

Two certified graders analyzed SDOCT scans using the InVivoVue viewing software (Leica Microsystems, IL). In the scan with first onset of edema, we graded across the fovea: severity of ME as mild, moderate, severe (Figure 1); elongated cystoid spaces; foveal contour (depressed, flat, or bulging); and photoreceptor bulging (upward bulging of the outer plexiform layer at foveal center). Quantitative measures included central foveal thickness (CFT, from the internal limiting membrane [ILM] to Bruch's membrane), foveal-parafoveal (FP) ratio (parafoveal thickness at 1000 μm from the fovea/CFT), and total retinal thickness measured at 500 μm , 1000 μm , 1500 μm and 2000 μm .

Statistical analyses were performed using SAS and JMP Pro 14 (SAS, NC). Onset of ME was compared with gestational age and birth weight using *t* tests. The Fisher exact test was used to test associations with systemic health factors. Continuous variables were assessed using an *F* test (score statistic) from a generalized estimating equation (GEE) model that accounted for use of both eyes in the analysis. Categorical variables were assessed using binary and multinomial logistic regression using GEE to account for the use of both eyes.

Results

Of the 40 preterm infants who were initially included, 11 with a history of treatment for ROP were excluded, as was 1 infant who lacked sufficient macular images to determine edema at onset. A total of 28 infants were included in the analysis: 20 in the early-onset and 8 in the late-onset group. Both eyes of all infants were included. All demographics, including mean gestational age and birth weight for the early- vs late-onset infants were comparable ($P=1.00$ and 0.65 , resp.). See Table 1. Edema appeared by 30 weeks' PMA in 3 early-onset infants. We found no significant relationship between age at onset of edema and most of the systemic factors known to influence health outcomes; the one exception was hydrocephalus, which was present in 1 infant in the early-onset group and 3 infants in the late-onset group ($P=0.05$).

We found a significant difference in the severity of ME at onset ($P=0.01$) between the two groups. Of the 40 eyes in the early-onset group, 13 (32%) had mild edema, 15 (38%) had

moderate edema, and 12 (30%) had severe edema. Of the 16 eyes in the late-onset group, 12 (75%) had mild edema and 4 (25%) had moderate edema; no eyes had severe edema at onset. We noted both elongated cystoid spaces and photoreceptor bulging only in the early-onset group (13/40 eyes [45%]). See Table 2. The foveal contour was bulging in 10 eyes (26%), flat in 10 eyes (26%), and depressed in 19 eyes (49%) in the early-onset group, whereas all 16 eyes in the late-onset group had a depressed foveal contour.

The CFT and FP ratio were significantly greater in the early-onset group than in the late-onset group (Table 2; $P = 0.0012$, $P = 0.002$, resp.). However, the retina was thinner, at 1000 μm , 1500 μm , and 2000 μm from foveal center, in the early-onset group ($P = 0.018$, $P = 0.007$, and $P = 0.004$, resp.). Central choroidal thickness did not vary significantly between the early and the late-onset groups ($P = 0.116$).

Discussion

We found that early-onset edema had a more severe morphology, with foveal bulging and elongated cystoid spaces than compared to late-onset edema, which presented as small cystoid spaces outside the foveal center. Reflecting this, CFT was thicker in early-onset edema, whereas the parafoveal retina was thicker in late-onset edema. The latter could also be affected by maturation, with thicker parafoveal retina expected at older PMA.

Prior studies have associated edema with suboptimal functional outcomes, suggesting that it may be a pathologic phenomenon.⁷ It has been suggested that edema in ROP may be due to vascular leakage secondary to vascular endothelial growth factor imbalances²; others have pointed to possible associations with vitreomacular traction,^{2,8} systemic disease,⁹ or poor neurodevelopmental outcomes, indicating that edema within the retina may reflect cellular events occurring in the brain.⁶ In adults, cystoid structures have been associated with neurologic pathology, such as optic atrophy secondary to either multiple sclerosis or hydrocephalus.¹⁰ Comparable to the adults, our late-onset group demonstrated a pattern of small cystoid spaces, which may also be suggestive of brain injury or even neuroinflammation. Despite the small numbers, infants in our late-onset group had a higher prevalence of hydrocephalus and necrotizing enterocolitis compared with the early-onset group.

Our study is limited by the small sample size, retrospective design, and smaller numbers in the late-onset group. Nevertheless, we identified significant morphological differences in ME based on age at onset. Future larger, prospective, longitudinal studies, such as BabySTEPS ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02887157), NCT02887157), exploring the onset, duration, and associations with systemic and neurological health, may clarify these early findings.

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FIG 1.

Representative spectral domain optical coherence tomography B-scans of macular edema in preterm infants with late-onset (A) and early-onset (B,C) edema. All cystoid spaces were found in the inner nuclear layer, and edema was categorized as follows: mild edema (A), defined as presence of cystoid spaces that cause little to no deformation of the foveal contour; note, these did not necessarily occur at the foveal center; moderate edema (B), with presence of cystoid spaces that cause either flattening or a slight upward bulging of the fovea and deformation of the foveal pit; and severe edema (C), with presence of cystoid spaces that cause severe upward bulging of the foveal contour. Moderate and severe edema show the presence of elongated cystoid spaces. Retinal layers: 1, retinal nerve fiber layer; 2, ganglion cell layer; 3, inner plexiform layer; 4, inner nuclear layer; 5, outer plexiform layer; 6, outer nuclear layer; 7, retinal pigment epithelium–photoreceptor complex; 8, choroid.

Table 1. Basic demographic information and systemic features of infants in the early-onset and the late-onset edema groups

Characteristic	Early onset (N = 20)	Late onset (N = 8)	P value
Gestational age, weeks, mean $\pm$ SD	25 $\pm$ 0.8	25 $\pm$ 1	1
Birth weight, g, mean $\pm$ SD	772 $\pm$ 139	746 $\pm$ 127	0.65
PMA, weeks, at OCT imaging that documented onset, mean $\pm$ SD	31.8 $\pm$ 1	39 $\pm$ 2	
PMA, weeks, at first OCT imaging, mean $\pm$ SD ^a	31 $\pm$ 0.8	32 $\pm$ 2	0.01
Time interval, weeks, between consecutive OCT sessions, no. (%) ^b			
0 (first imaging)	11 (55)	0	
1	7 (35)	5 (63)	
2	2 (10)	2 (25)	
3	0	1 (12)	
Sex, no. (%)			1
Male	11 (45)	4 (50)	
Race, no. (%)			0.8
African American	10 (50)	5 (63)	
White	6 (30)	2 (25)	
Mixed	3 (15)	1 (13)	
Asian	1 (5)	—	
Systemic features, no. (%)			
Intraventricular hemorrhage	6 (30)	4 (50)	0.40
Bronchopulmonary dysplasia	3 (15)	3 (38)	0.31
Patent ductus arteriosus	8 (40)	2 (25)	0.66
Indomethacin use	10 (50)	3 (38)	0.68
Hydrocephalus	1 (9)	3 (38)	0.05
Necrotizing enterocolitis	0	2 (25)	—
Pulmonary edema	6 (30)	2 (25)	1
Pulmonary hypertension	0	1 (13)	—

OCT, optical coherence tomography; *PMA*, postmenstrual age; *ROP*, retinopathy of prematurity; *SD*, standard deviation.

Although we pursued enrollment of all infants who were eligible for ROP screening, parents sometimes consented to study participation later in the nursery course of screening for ROP and after infant transfer to our nursery. Infants were imaged at the time of each ROP examination until they left the nursery or withdrew from the study.

^q OCT imaging matched the ROP examination interval, except for 1 infant with a 3-week gap.

Table 2.

Morphological characteristics and quantitative assessment of the severity of macular edema in the early-onset versus late-onset preterm infants

Variable	Early onset (N = 40)	Late onset(N = 16)	P value
Qualitative features ^a			
Severity of macular edema, no. (%)			0.01
Mild	13 (32)	12(75)	
Moderate	15 (38)	4 (25)	
Severe	12 (30)	0	
Appearance of foveal contour, no. (%)			-
Depressed	19 (49)	16 (100)	
Flat	10 (26)	0	
Bulging	10 (26)	0	
Presence of elongated cysts, no. (%)	13 (45)	0	-
Presence of photoreceptor bulging, no. (%)	13 (45)	0	-
Quantitative features, mean $\pm$ SD			
Central foveal thickness μm	160 $\pm$ 44	122 $\pm$ 21	0.012
Foveal-parafoveal ratio	1.02 $\pm$ 0.26	0.63 $\pm$ 0.15	0.002
Retinal thickness at 500 μm	165 $\pm$ 25	182 $\pm$ 31	0.192
Retinal thickness at 1000 μm	158 $\pm$ 23	201 $\pm$ 40	0.018
Retinal thickness at 1500 μm	146 $\pm$ 20	192 $\pm$ 37	0.007
Retinal thickness at 2000 μm	138 $\pm$ 17	180 $\pm$ 27	0.004
Central choroidal thickness	132 $\pm$ 29	159 $\pm$ 50	0.116

SD, standard deviation.

^aP value not reported as one of the groups did not have any positive response.