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Comparison of Ultrasonic and Ophthalmoscopic Evaluation of Retinopathy of Prematurity

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Abstract

Purpose—Screening for detection of retinopathy of prematurity (ROP) currently is limited to indirect ophthalmoscopy, which requires considerable examiner skill and experience. We investigated whether conventional 10 MHz B-scan ultrasonography could document the clinical stages of ROP as accurately as indirect ophthalmoscopy.

Methods—Thirty-four eyes of 18 neonates were examined by masked, independent observers with indirect ophthalmoscopy and digitally recorded 10-MHz B-scan ultrasonography. After pupil dilation and lid speculum placement, the retinologist recorded the stage of retinopathy with a retinal drawing. The ultrasonographer, without use of papillary mydriatics or lid speculum, determined the presence or absence of a ridge or tractional elements, if present on the ridge.

Results—Ultrasound grade correlated with clinical grade ($R = .79$, $P < .001$). However, nine eyes were overdiagnosed by one stage, and one eye, in which a peripheral detachment was mistaken for an artifact, was underdiagnosed.

Conclusions—Ten-megahertz ultrasonography offers the potential of imaging and detecting the clinical stages of ROP; the use of higher ultrasound frequencies, now becoming commercially available, is likely to enhance diagnostic accuracy. Care must be taken to distinguish between artifact and true anatomical structures in noncontact ultrasound examinations. Neonates with suspected ROP could be screened with B-scan ultrasonography by neonatal personnel without pupillary dilatation or lid speculum, thus eliminating potential morbidity, and clinically significant cases of ROP then could be referred to the retinologist.

Introduction

The early detection of retinopathy of prematurity (ROP) in neonates with a gestational age ≤ 28 weeks and birth weight $\leq 1,500$ g is crucial for successful management.^{1–3} These evaluations require pupillary dilation, often with use of a lid speculum, are time consuming and expensive, and also carry a risk for morbidity.^{1–4}

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Ultrasound offers another means for screening for the presence of ROP. B-scan ultrasonography can provide real-time cross-sectional images of the globe through the closed eyelid, thereby eliminating the need for pupillary mydriasis and use of a lid speculum. Currently, a frequency of 10 MHz is the standard for ophthalmic ultrasonography as 10 MHz probes can readily detect retinal detachment and vitreoretinal tractional membranes. With a 200- μ m axial resolution, the retinal ridge characterizing stage 2 disease also might be detectable as well. Given these capabilities and the noninvasive nature of the examination procedure, we designed this study to examine the capacity of B-scan ultrasound to detect and characterize ROP.

Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards of the Columbia Presbyterian Medical Center, Weill Medical College of Cornell University, and New York Medical College. Informed consent was obtained from parents of the infants.

Between March and November 2002, 18 infants with birthweight < 1,500 g or a gestational age < 32 weeks were examined consecutively at Babies Hospital, Columbia Presbyterian Medical Center. Gestational age was determined by the neonatologist caring for the infant from a best estimate of the mother's last menses and obstetrical history, and the infant's neonatal examination.

Ophthalmoscopic Evaluation

Screening dilated ophthalmoscopic evaluations using 0.5% cyclopentolate and 2.5% phenylephedrine drops for pupillary mydriasis administered 1 hour prior to the examination were performed. A lid speculum was used for retinal viewing. A scleral depressor was used when necessary, and a retinal sketch with indirect ophthalmoscopy using a 25-D lens was made of the central and peripheral retina.

Clinical stages were defined as follows:

- Stage 0: immature retinal vasculature only,
- Stage 1: retinal pigment demarcation line,
- Stage 2: retinal ridge,
- Stage 3: retinal ridge with vitreoretinal traction secondary to neovascularization,
- Stage 4: retinal detachment, and
- Stage 5: closed cone retinal detachment.

Ultrasonic Evaluation

Ultrasonically, we did not attempt to diagnose threshold or plus disease as our goal was primarily to identify all stages of ROP that would warrant a retinologist's examination for intensive follow up, particularly commencing with stage 2 ROP, if ultrasound were used as the sole screening device.

Ultrasound examination was performed at cribside on the same neonates who underwent ophthalmoscopic evaluations. Thirty-four eyes of 18 children were scanned: in one case, parental consent was only given for one eye, and in another instance, ultrasound data inadvertently were not recorded in one eye. The scanning system used a 10-MHz mechanical sector probe that was offset from the eye by placing it in a thin latex sheath filled with sterile

normal saline solution. After placing one or two drops of methylcellulose on the eyelid, the sheath was then placed in contact with the eyelid and the transducer focal plane placed in the region of the equator (Fig. 1).

The examination was performed without general or local or topical anesthesia; neither a lid speculum nor iris dilating drops were used. The examination was recorded on a digital video recorder for subsequent review. Recording of real-time video, rather than static images, helped to overcome the effects of eye and head movement on the ultrasonic image. Recorded ultrasound data were reviewed carefully for the presence of diagnostically significant pathology and graded accordingly.

Ultrasound images digitally recorded in real time were reviewed subsequent to the examination, without the ultrasound examiner being informed of the clinical stage determined in the prior examination by the retinologist. The presence of the following features on ultrasound was considered significant:

- An acoustic reflex at the periphery of the posterior pole suggestive of zone 1 ROP,
- An acoustic reflex suggestive of a ridge in the region between the ciliary body and equator (ultrasound zone 2, stage 2),
- Elevation or layer separation in the anterior retinal ridge region (ultrasound zone 2, stage 3),
- Presence of retinal detachment (ultrasound zone 2, stage 4), and
- Presence of a closed-cone retinal detachment (ultrasound stage 5).

Eyes without clear evidence of any of these features were classified as stage 1, recognizing that this also could encompass clinical stage 0. Representative ultrasonograms are presented in Figure 2.

Correlation of Ophthalmoscopic and Ultrasonic Evaluations

Data from the clinical ophthalmologist's retina examination were coded as to the presence or absence of ROP. If ROP was present, the stage, zone, and presence or absence of plus disease were noted. Data from the ultrasonic evaluation were evaluated and graded according to the international classifications.⁵ Three observers correlated the data from the ophthalmic and ultrasound results; these were tabulated with zone and stage classification of ROP reached by consensus.

Statistical analysis of ultrasound and retinal examination results was performed. Ultrasound was cross-tabulated with retinal grade and the correlation coefficient between these grades was determined.

Results

The characteristics of the study population broken down by clinically determined stage of ROP for each eye is summarized in Table 1. No cases of stage 5 ROP or zone 1 ROP were found.

Table 2 provides a cross-tabulation between the clinical stage and the ultrasound-determined stage. The null hypothesis of this being a random distribution is rejected (two-sided Pearson chi-square statistic = 43.1, $P < .001$). Because the clinical stage of left and right eyes of the same patient may not be independent, left and right eye findings were analyzed separately. In both cases, chi-square values showed statistical significance ($P < .05$).

The correspondence between acoustic and clinical stages is presented in Figure 3. There was a high degree of correlation between the ultrasound and clinical stages (Pearson $R = .79$, $P < .001$).

Discussion

Current guidelines for laser treatment of ROP have been established for more than a decade, yet despite optimal retinal ophthalmoscopic screening and earlier treatment of at-risk infants, visual morbidity from ROP still occurs.¹ In the United Kingdom, 9% to 12% of babies treated between 1992 and 1994 became blind in one eye and 5% each year became blind bilaterally.² The 10-year follow up from the CRYO-ROP study showed fewer unfavorable outcomes in treated versus control eyes (49.4% versus 62.1%) and visual acuity of 20/40 or better in cryotherapy-treated eyes equal to that of control eyes. Nevertheless, a disturbing 22% receiving cryotherapy treatment still went on to retinal detachment, compared to 41.4% of untreated control eyes.² The ongoing Early Treatment for ROP Study is examining whether earlier treatment of ROP may improve these outcomes further, prior to the attainment of threshold ROP even with optimal screening, but results await the completion of the study. Current screening guidelines for treatment with cryotherapy or laser therapy involve attainment of threshold disease, defined as 5 or more contiguous or 8 accumulative clock hours of stage 3 ROP in either zone 1 or zone 2 in the presence of “plus” disease. Currently, screening guidelines are limited to infants born ≤ 28 weeks postmenstrual age and birthweight $\leq 1,500$ g.⁵ Using this relatively restrictive screening criteria would have missed 4% of infants with birth weights between 1,500 and 2,000 g who developed zone 2, stage 1 or stage 2 ROP and 0.6% who displayed zone 2, stage 3 ROP.⁴

While treatment cost effectiveness has been demonstrated,^{5,6} risk factors for identification of infants $\geq 1,500$ g have been left to the individual clinician to define.⁷ Furthermore, screening examinations are time consuming, labor intensive, and not without risks, both cardiovascular and respiratory, that have the possibility of serious morbidity.⁴

B-scan ultrasonography allows imaging of the eye and orbit without the need for mydriatic drops or a lid speculum. Conventional 10 MHz handheld probes provide an axial resolution of approximately 200 μm . These probes are generally focused at 20 to 25 mm, such that their focal zone in a contact examination (using ultrasound gel with a closed eyelid) will fall near the retina in an adult eye. Ultrasound biomicroscopy, in which frequencies of approximately 50 MHz are used, can provide much better resolution (approximately 30 μm) but is affected to a greater extent by attenuation, which increases exponentially with frequency. For this reason, ultrasound biomicroscopy examinations are performed with a waterbath with the eyelids held open by a lid speculum or fluid-filled eyecup that also acts as a lid speculum. In a neonate, such a procedure would require constraint and possibly general anesthesia, which are potential sources of morbidity.

To minimize potential morbidity, we elected to use a conventional 10-MHz probe, rather than ultrasound biomicroscopy. To compensate for the inappropriate focal length of the probe, we placed the probe in a fluid-filled sheath in apposition to the skin of the lateral canthus, which allowed placement of the focal zone in the region of interest for ROP, the temporal retinal periphery. Scanning was performed without anesthesia, mydriatic drops, or a lid speculum.

We performed a masked trial using B-scan ultrasonography to determine whether ocular ultrasonic mass screening of potentially “at-risk” infants at a referral neonatal center was comparable to indirect ophthalmoscope diagnosis of stages 1 through 4 ROP. Thirty-four eyes of 18 neonates were examined. The ultrasonic stages were in agreement with the ophthalmoscopic findings in 24 eyes, overdiagnosed in 9 eyes, and underdiagnosed in 1 eye.

In the one eye that was underdiagnosed, a stage 4 ROP was misclassified as stage 2. On review of the recorded ultrasound after the clinical diagnosis was provided, we found that a detached retina in the temporal periphery not involving the posterior pole (ROP stage 4A) was mistaken for a reduplication artifact. This illustrates the care required to differentiate artifactual reduplication echoes that are generated in noncontact standoff scanning procedures such as that used in this study, in which anterior segment structures may generate ghost echoes in mid-vitreous.

During ultrasound examination, this type of artifact can be differentiated from true anatomic structures by adjusting the position of the probe in the anteroposterior direction within the water-filled sheath while the potential artifact is visible. When this procedure is performed, the displayed image of the eye shifts the same distance as the probe, but artifacts shift twice the distance of the shift of the probe. Thus, the artifact shifts in position relative to the true anatomy displayed in the ultrasound image, whereas any pathological structure, being part of the true anatomy of the eye, will not shift. In this case, we readily concluded that an echo pattern was artifactual, illustrating the care required to make a reliable distinction.

The ultrasonic grade was correlated with the clinical grade ($R = .79$, $P < .001$). In two of the stage 4 eyes, the patient's retinal condition was recognized by clinical ophthalmoscopy prior to our examination and subsequent retinal surgery was performed. Our study was limited in that it did not include infants with zone 1 disease, not by design but because of their absence during the study period. For the same reason, no stage 5 ROP infants were examined. Further, we suspect that the low frequency 10-MHz probe would, only with difficulty, visualize the nonelevated border that is often present with zone 1 stage 3 ROP disease.

Ultrasound biomicroscopy is capable of producing diagnostically significant images in ROP eyes with far higher resolution than that obtainable using the 10-MHz probe used in this study.⁸ However, ultrasound biomicroscopy technology uses a nonenclosed probe and frequency (50 MHz) that cannot penetrate the eyelid. Recently, ultrasound systems with enclosed handheld probes of 15 to 20 MHz have become available, and these may help to bridge the gap between ultrasonic penetration and resolution. These technologies might improve ultrasonic resolution so that zone 1 stage 3 border might be visualized. We recently began studies of ROP in this frequency range. Other noninvasive screening techniques using the RetCam 120 camera yielded a positive predictive value of 96.6%, but there were 12 false-negative and 2 false-positive results and discrepancies with regard to plus disease.^{9,10}

We believe the potential for screening infants for ROP lies in the speed, simplicity, and accuracy of a technique that can identify "at-risk" eyes¹¹ for referral by neonatal personnel to retinologists, thereby eliminating the morbidity and time-consuming retinal screenings associated with indirect ophthalmoscopy.

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Figure 1.
Cribside examination of the eye with ultrasound. Enclosure of the transducer probe in a fluid-filled sheath ensures sterility and allows optimal positioning of the transducer focal zone.

Figure 2.

(A) Ultrasonic view of an eye with stage 2 retinopathy of prematurity (ROP). The arrows point to a ridge, which exhibits increased echogenicity. (B) Ultrasonic view of a peripheral detached retina (arrows) in the region of a ridge in stage 4 ROP.

Figure 3.
Histogram representing comparative ultrasound and clinical classification of all eyes.

TABLE 1

Distribution of Eyes by Clinical Stage of Retinopathy of Prematurity

Clinical Stage	No. (%)
0-1	26 (76.5)
2	2 (5.9)
3	4 (11.8)
4	2 (5.9)
Total	34 (100.1)

TABLE 2

Distribution of Ultrasound Stage Versus Clinical Stage

Ultrasound Stage	Clinical Stage			
	0-1	2	3	4
0-1	18			
2	8	2		1
3			3	
4			1	1