Image analysis of posterior pole vessels identifies type 1 retinopathy of prematurity

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Identification of type 1 retinopathy of prematurity (ROP) relies heavily on the presence of characteristics of plus disease, especially tortuosity. However, a relatively infrequent subset of eyes with type 1 ROP, eyes with zone 1, stage 3 ROP without plus disease, is included in treatment indications. We examined if posterior pole vessel width is associated with type 1 ROP in a subset of eyes with zone 1, stage 3 ROP without plus disease and whether vessel width differentiates type 1 from non–type 1 ROP.

Treatment of eyes with type 1 ROP is based on results from the Early Treatment for Retinopathy of Prematurity (ETROP) Study.[1,2] Type 1 ROP consists of the following: (1) any ROP in zone 1 with plus; (2) zone 1, stage 3 ROP without plus; and (3) zone 2, stage 2 or 3 ROP with plus disease.[1,2] The ETROP Study investigators recommended treatment for eyes with type 1 ROP, which includes all eyes with plus disease (except for zone 2, stage 1) and eyes with zone 1, stage 3 ROP without plus disease.[1,2] The presence of plus disease, a subjective clinical diagnosis made by comparison with standard reference photographs, is an essential component of 2 of the 3 categories of type 1 disease.

With the emphasis on eyes with plus disease as the current indication for ROP treatment, vascular changes in a subset of type 1 ROP—specifically those with zone 1, stage 3 ROP without plus disease—may be missed. We wanted to determine whether posterior pole vessel width using narrow-field images could identify eyes with zone 1, stage 3 ROP without plus disease and whether those changes differentiate type 1 from non–type 1 ROP.

Subjects and Methods

We conducted a retrospective case-control study. Institutional review board approval was obtained. ROP status was classified based on the diagnosis recorded by 3 pediatric ophthalmologists. Plus diagnosis was determined on clinical examination by comparison with a reference photograph.[1] Three groups were based on the presence of type 1 ROP. Five babies were defined as cases with eyes with type 1 ROP (zone 1, stage 3) without plus disease. Two groups of controls were defined as type 1 ROP with plus disease (8 babies) and non–type 1 ROP (17 babies). Controls were selected based on their similarity to cases with regard to gestational age, birth weight, postmenstrual age, gender, and race. We utilized the NM200D (Nidek, Inc., Aichi, Japan), a noncontact 30° fundus camera.

For those infant eyes with type 1 disease, images obtained prior to laser photocoagulation were selected. For eyes of infants in the group without type 1 ROP, images obtained closest to the postmenstrual age and birth weight of the corresponding cases (type 1 ROP without plus) were selected. The averages for gestational age (24.6-24.9 weeks), postmenstrual age (33.2-33.5 weeks), and birth weights (659–677 g) were similar. All images were de-identified, assigned an arbitrary study identifier, randomized, and unpaired. Images were analyzed as obtained (with no alteration of orientation or contrast) using Vasculo-matic ala Nicola version 1.1 (IVAN, Department of Ophthamology and Visual Science, University of Wisconsin–Madison, Madison, WI), a semi-automated image analysis software, to measure width.[3-5]

For comparison of vessel caliber, inter-eye correlations between measures from paired eyes were adjusted by generalized estimating equations. Analysis of variance established similar demographic characteristics and tested differences among the 3 groups in vessel caliber for arterioles, venules, and combined vessel caliber. Post hoc pairwise comparisons were performed when the test of any difference was significant ($p < 0.05$). The Hochberg procedure (a less conservative and more powerful procedure than Bonferroni method) adjusted p-values from multiple pairwise comparisons and controlled the overall type 1 error (0.05, 2 sided).[6] All statistical analyses were conducted in SAS version 9.1 (SAS, Inc., Cary, NC).

Results

Table 1 displays mean vessel width increasing progressively among eyes without type 1 ROP, type 1 ROP without plus, and type 1 ROP with plus disease. A significant difference among the 3 groups was noted when venules alone ($p = 0.01$) and venules and arterioles ($p = 0.02$) were considered. Controls with type 1 and those without type 1 were significantly different for venules alone ($p = 0.003$) and both arterioles and venules ($p = 0.003$). When both groups of type 1 ROP eyes were compared, there were no significant differences for vessel width, with only a 2.7 μm difference in venule width between type 1 ROP

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Deepika N. Shah was supported by the Doris Duke Clinical Research Fellowship.

The authors have no conflicts of interest to disclose.

Submitted February 11, 2009.

Revision accepted July 9, 2009.

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J AAPOS 2009;13:507-508.

1091-8531/2009/$36.00 + 0

doi:10.1016/j.jaapos.2009.07.004

Table 1. Comparison of vessel width among eyes with type 1 ROP (with and without plus disease) and non–type 1 ROP

	Mean ± SE*				Multiple comparisons adjusted *p-value*†		
	Cases with type 1 ROP without plus disease) (n = 5)	Controls with type 1 ROP with plus disease (n = 8)	Controls without type 1 ROP (n = 17)	Overall *p-value*	Cases vs controls with type 1 ROP with plus disease	Cases vs controls without type 1 ROP	Controls with type 1 vs controls without type 1 ROP
Arteriole (μm)	73.4 ± 2.2	80.2 ± 4.6	67.4 ± 2.7	0.07	0.18	0.16	0.06
Venule (μm)	101.4 ± 7.0	104.1 ± 5.3	84.4 ± 2.9	0.01	0.76	0.052	0.003
All vessels (μm)	87.4 ± 3.8	91.5 ± 3.3	77.7 ± 2.6	0.02	0.41	0.07	0.003

*Mean and SE are in arbitrary units.
†Using the Hochberg procedure.

eyes with and without plus disease. Although the mean values for vessel width suggest a difference between type 1 eyes without plus disease and controls without type 1 ROP (particularly for venules with a 17 μm difference), these results were not statistically significant ($p = 0.07$).

Discussion

Due to the restricted field of the fundus in narrow-field images, it is speculated that remote evaluation of its images may result in higher false-negative rates in detecting serious ROP, especially among zone 1 ROP without plus disease. The primary purpose of this study was to determine whether image analysis of eyes with type 1 ROP without plus disease could be distinguished from those eyes without type 1 ROP and, secondarily, from eyes with type 1 ROP with plus disease. We report that, based on a comparison of vessel width, the group of the ten eyes with type 1 ROP without plus disease can be distinguished from eyes without type 1 ROP. Given the marginal statistical significance after adjustment of multiple comparisons (adjusted $p = 0.07$) we acknowledge that this difference may be due to chance alone.

We found no statistically significant difference between mean vessel width of eyes with type 1 ROP without plus disease and eyes without type 1 ROP. However, we found that mean vessel width was greater for type 1 ROP without plus disease relative to eyes without type 1 ROP. Interestingly, when we compared our cases to eyes with type 1 ROP with plus disease, we found a very small difference in the mean vessel width between the 2 groups, which was not significant. Although vessel width abnormalities measured in type 1 ROP eyes without plus disease may not be sufficient to qualify on clinical examination as plus disease, they are sufficiently abnormal to be distinguished from eyes without type 1 using image analysis. Quantitative measurement of vessel changes associated with ROP may be more consistent and reliable than the clinical judgment required for the diagnosis of plus disease, a basically binary decision.[7-9]

There were several limitations to our study. Results from eye examinations were used as reference standards and, despite efforts to standardize clinical judgment of plus disease across examiners, inter-expert disagreement on diagnosis of plus disease is significant.[7-9] Furthermore, ETROP recommendations do not suggest treatment of all eyes with plus disease, as in zone 2, stage 1 ROP and zone 3 ROP with plus disease.[1,2]

In conclusion, in our small sample, we found no significant differences on analysis of narrow-field digital images of eyes with type 1 ROP without plus disease from those without type 1 ROP, although a clear trend toward increased width of vessels was present in eyes with type 1 ROP without plus disease. Further study with a larger sample size of stage 3 zone 1 ROP without plus disease is necessary but can be difficult given its relatively low incidence.

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