Risk Stratification of Preplus Retinopathy of Prematurity by Semiautomated Analysis of Digital Images

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Objective: To determine whether quantitative analysis of retinal vessel width and tortuosity from digital images discriminates which eyes with preplus retinopathy of prematurity (ROP) progress to treatment severity.

Methods: Posterior pole images of eyes at first clinical diagnosis of preplus ROP were obtained using a 30°-field, noncontact fundus camera. Width and tortuosity of retinal vessels were analyzed from digital images using computer-assisted image analysis software. Mean width and tortuosity of venules and arterioles were compared in 19 preplus eyes that regressed spontaneously and 11 preplus eyes that progressed to treatment severity. Receiver operating characteristic curve analysis was performed to assess whether width and tortuosity discriminated between groups.

Results: Mean widths of venules alone, arterioles alone, and the 3 widest vessels were higher in preplus progressed eyes ($P < .04$). Mean tortuosity of the 3 most tortuous vessels was higher in preplus progressed than in preplus regressed eyes ($P = .01$). Most vessel width and tortuosity variables predicted which eyes with preplus progressed to treatment moderately well, with an area under the receiver operating characteristic curve of 0.72 to 0.82.

Conclusions: Digital image analysis of retinal vessel width and tortuosity may be useful in predicting which preplus ROP eyes will require treatment. Because vascular abnormalities are a continuum and clinical diagnosis is subjective, quantitative analysis may improve risk stratification for ROP.


Retinopathy of prematurity (ROP) is a disorder of abnormal development of retinal vessels in premature low-birth-weight babies. Abnormal dilatation and tortuosity of posterior pole retinal vessels, or plus disease, is a primary driver in the decision to treat ROP. Carefully timed ablation of the peripheral retina is necessary to decrease the likelihood of retinal detachment and blindness.

The diagnosis of plus disease, however, is subjective given that it is based on comparison with a "reference" photograph from more than 20 years ago and relies on the individual physician's overall interpretation. Interexpert agreement regarding the diagnosis of plus disease is poor. Reflecting the fact that vascular changes in ROP are on a continuum, Wallace et al determined that early vascular dilatation and tortuosity insufficient for plus disease had prognostic significance for ROP. They proposed that such "mild" dilatation and tortuosity, or "preplus" vascular changes, may have clinical and research relevance. In "The International Classification of Retinopathy of Prematurity Revisited," preplus ROP was defined as vascular abnormalities insufficient for the diagnosis of plus disease but that present with more arterial tortuosity and more venous dilatation than expected in the normal preterm eye.

The diagnosis of this intermediate state of vascular abnormalities in ROP also remains subjective. Similar to plus disease, the diagnosis of preplus ROP shows interobserver variability among pediatric ophthalmologists in the judgment of presence or absence of disease from cropped clinical photographs of premature retinas. For this reason, the development of a quantitative method for grading vascular changes in ROP may be helpful. One such approach, computer-assisted analysis of digital images obtained from infants at risk for ROP, has achieved promising results. Computer-Assisted Image Analysis of the Retina is a recently described technique that semiautomatically detects retinal vessels and measures dilatation and tortuosity from digital images of the posterior pole. Herein, we report on the ability of computer-assist-
ted digital image analysis of retinal vessel width and tortuosity to discriminate which eyes having an initial diagnosis of preplus ROP will progress to treatment severity.

METHODS

IMAGE ACQUISITION

A database of digital images was established as part of a larger longitudinal project examining digital fundus photography in neonates at risk for ROP at the neonatal intensive care units of the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania, Philadelphia. Institutional review board approval was obtained from both hospitals, and the parents of all study participants provided informed consent. Eyes were dilated using a combination of tropicamide, 1%, and phenylephrine, 2.5%, and the posterior poles were imaged using a 30°-field, noncontact fundus camera (NM-200D; Nidek Inc, Aichi, Japan). After image acquisition, each infant underwent dilated fundus examination using indirect ophthalmoscopy by an expert pediatric ophthalmologist (M.D.M. or G.E.Q.). Infants were followed up clinically until the eye was treated with panretinal photocoagulation or showed regression of ROP.

IMAGE SELECTION

The database was reviewed for infants who were diagnosed as having preplus ROP on clinical examination between March 1, 2005, and August 31, 2008. Infants with zone 1 (the center of which is the optic nerve) ROP and infants whose preplus eye was treated before type 1 ROP severity were excluded from this study. An image from the date of earliest diagnosis of preplus ROP was selected for each participant. The single highest-quality image from the right eye was chosen. In cases of asymmetrical ROP, the left eye was chosen only if the right eye never received a diagnosis of preplus disease. Digital image quality was assessed on the following variables: (1) centering of the optic disc, (2) contrast between retina and vessels (focus), and (3) image brightness. For perspective, images from 2 other groups of infants were selected: (1) eyes that never developed ROP and (2) eyes that developed plus ROP without an initial diagnosis of preplus. In addition, nonparametric receiver operating characteristic (ROC) curve analysis was performed to assess whether vessel width and tortuosity could discriminate between preplus eyes that regressed and preplus eyes that progressed. Comparison of means and proportions was performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), and calculations of the area under the ROC curve and its 95% confidence interval were performed using STATA version 10.0 (StataCorp LP, College Station, Texas).

DATA ANALYSIS

Vessel variables (width and tortuosity) were examined in several ways to present an exploratory descriptive analysis of vessel changes in preplus ROP that progresses vs regresses. First, mean width and tortuosity based on all vessels were calculated for each eye. Second, to determine whether overall vessel changes depended on vessel type or on the most abnormal vessels only, 2 subanalyses were conducted. Vessel type subanalysis involved the calculation of mean width and tortuosity for arterioles alone and venules alone for each eye. Another subanalysis identifying the most abnormal eye involved calculation of the mean width of the 3 widest vessels from all analyzable vessels and the mean tortuosity of the 3 most tortuous vessels from all analyzable vessels from each eye. Each vessel variable was compared between preplus ROP eyes that regressed spontaneously and preplus ROP eyes that progressed to treatment using 2-sample t tests. Owing to the exploratory nature of the analysis, multiplicity adjustments on P values were not made, and all comparisons performed were presented. For perspective on the clinical diagnosis of preplus, mean width, mean tortuosity, and the proportion of each vessel type (arteriole and venule) composing the 3 widest and the 3 most tortuous vessels were compared with 2 other groups: (1) eyes that never developed ROP and (2) eyes that developed plus ROP without an initial diagnosis of preplus. Of the 142 infants in the larger longitudinal project, 39 had a clinical diagnosis of preplus ROP. Two infants with preplus ROP were excluded because there were no images for the day of initial diagnosis of preplus ROP. Five infants were excluded because they received early treatment before regressing spontaneously or reaching commonly accepted treatment severity. Two infants were excluded because they had zone 1 ROP. Thus, there were 30 eligible infants who had a clinical diagnosis of preplus ROP in zone 2 (a doughnut-shaped area surrounding zone 1) in 1 or both eyes. Images from 30 eyes of 30 infants (28 right eyes and 2 left eyes) were selected for analysis. Of the 30 eyes with preplus ROP, 19 regressed spontaneously and 11 progressed to treatment. The mean (SE) interval between the initial diagnosis of preplus and treatment was 7.91 (1.28) days. Mean gestational age, birth weight, sex, race, postmenstrual age, and weight when preplus was first diagnosed were not significantly different between groups.

Vessel type subanalysis is given in Table 1. The mean widths of venules alone and arterioles alone were significantly higher in the sample of eyes in which preplus progressed than in eyes in which preplus regressed (P = .02...
Table 1. Mean (SE) Width and Tortuosity of Retinal Vessels in Preplus Eyes That Regressed Spontaneously vs Preplus Eyes That Progressed to Treatment Severity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preplus Regressed Eyes (n=19)</th>
<th>Preplus Progressed Eyes (n=11)</th>
<th>Difference (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width of all vessels</td>
<td>5.34 (0.22)</td>
<td>5.59 (0.12)</td>
<td>0.25 (-0.37 to 0.87)</td>
<td>.33</td>
</tr>
<tr>
<td>Width of venules alone</td>
<td>6.10 (0.23)</td>
<td>7.10 (0.31)</td>
<td>1.00 (0.21 to 1.79)</td>
<td>.02</td>
</tr>
<tr>
<td>Width of arterioles alone</td>
<td>4.11 (0.16)</td>
<td>4.58 (0.12)</td>
<td>0.47 (0.01 to 0.94)</td>
<td>.04</td>
</tr>
<tr>
<td>Width of the 3 widest vessels</td>
<td>6.69 (0.25)</td>
<td>7.59 (0.28)</td>
<td>0.90 (0.10 to 1.70)</td>
<td>.03</td>
</tr>
<tr>
<td>Tortuosity of all vessels</td>
<td>17.58 (1.93)</td>
<td>22.97 (2.89)</td>
<td>5.39 (-1.48 to 12.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Tortuosity of arterioles alone</td>
<td>19.95 (3.37)</td>
<td>25.81 (2.46)</td>
<td>5.86 (-4.03 to 15.8)</td>
<td>.22</td>
</tr>
<tr>
<td>Tortuosity of venules alone</td>
<td>15.16 (1.27)</td>
<td>18.55 (5.38)</td>
<td>3.39 (-5.57 to 12.4)</td>
<td>.55</td>
</tr>
<tr>
<td>Tortuosity of the 3 most tortuous vessels</td>
<td>31.02 (3.58)</td>
<td>45.86 (3.88)</td>
<td>14.86 (3.44 to 26.2)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a Width is measured in pixels and tortuosity is measured in arbitrary units.

b From 2-sample t tests.

Table 2. Vessel Types Composing the 3 Most Tortuous and the 3 Widest Vessels in Preplus Eyes That Regressed Spontaneously vs Preplus Eyes That Progressed to Treatment Severity

<table>
<thead>
<tr>
<th>Vessels, No. (%)</th>
<th>Preplus Regressed Eyes (n=19)</th>
<th>Preplus Progressed Eyes (n=11)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description of the 3 most tortuous vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriole</td>
<td>27 (48)</td>
<td>25 (76)</td>
<td>.01</td>
</tr>
<tr>
<td>Veneule</td>
<td>29 (52)</td>
<td>8 (24)</td>
<td></td>
</tr>
<tr>
<td>Description of the 3 widest vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriole</td>
<td>9 (16)</td>
<td>5 (15)</td>
<td>.91</td>
</tr>
<tr>
<td>Veneule</td>
<td>47 (84)</td>
<td>28 (85)</td>
<td></td>
</tr>
</tbody>
</table>

a n=56.

b From χ² tests.

The abnormal dilatation and tortuosity of retinal vessels in eyes with acute-phase ROP, or plus disease, is a valu-
able indicator of the severity of ROP. Plus disease is graded as present or absent. The binary nature of the diagnosis does not allow for inclusion of the important information that could be obtained from examining the spectrum of possible vascular changes in the developing retina. The utility of an intermediate diagnosis, such as preplus disease, has been incompletely studied. Wallace et al\(^8\) showed that early vascular dilatation and tortuosity not meeting the criteria for plus disease had prognostic significance in the early course of ROP. Despite introduction of the term and its progressive incorporation into diagnostic vernacular, the diagnosis of preplus ROP is a subjective determination of the physician, and agreement among pediatric ophthalmologists regarding the diagnosis of preplus and plus disease is poor.\(^5,7\) Consequently, the Cryotherapy for Retinopathy of Prematurity Study\(^9\) recommended the development of a quantitative way to grade vascular abnormalities of the posterior pole.

Advances in practical digital cameras for acquiring retinal images of at-risk infants and computer-assisted analysis of images may allow the application of quantitative analysis in ROP. Several studies\(^8-17\) have examined the validity, reliability, and feasibility of digital image analysis in detecting plus disease in ROP. Heneghan et al\(^11\) and Wallace et al\(^12,16,17\) established sensitive and specific thresholds for plus disease in ROP using semiautomated vessel analysis systems. To our knowledge, however, no studies have applied computer-assisted retinal analysis to examine the progression of preplus ROP. The objective of this study was to evaluate whether computer-assisted digital image analysis of retinal vessels is useful in predicting which eyes with preplus will progress to plus ROP requiring treatment.

These results indicate that computer-assisted analysis of retinal vessel width and tortuosity discriminates groups of eyes with an initial diagnosis of preplus ROP that will progress to treatment severity. As a group, preplus eyes that progress to treatment have greater width and tortuosity of retinal vessels than do preplus eyes that regress. Mirroring accepted clinical observations, quantitative measurements of venular width and arteriolar tortuosity were higher for more severe disease.

Most abnormal vessel subanalysis showed that the most dilated vessels and the most tortuous vessels were best able to highlight differences between the 2 groups of eyes. The selection of vessels for analysis by the operator is one of the most variable aspects of semiautomated analysis. Wallace et al\(^12,16,17\) explained how ROPtool was unable to choose consistently the most important vessels for each quadrant without operator input. Because it is debatable whether the smallest vessels on an image are actually choroidal vessels, comparing only the most abnormal vessels from all vessels identified by the program may improve the accuracy and reliability of retinal vessel measurements. Even without this adjustment, vessel width, but not tortuosity, was significantly different between groups. The decision to average the 3 most abnormal vessels vs selecting a different number of vessels to average is arbitrary and is based on our impression that in most cases, at least 3 vessels can be clearly identified as retinal vessels. A quadrant-based subanalysis is not presented because such labeling requires extensive grader input, introducing a greater possibility of selection bias. In addition, such input may not be practical for eventual clinical implementation of an automated image analysis system. Nevertheless, as software algorithms and vessel detection systems improve, we expect that other subanalyses, such as tortuosity of arterioles alone, may aid in the evaluation of which eyes with preplus disease are at risk for vision-threatening ROP.

In addition to width and tortuosity, the present results indicate that the distribution of vessel type that composes the most tortuous vessels may help with risk stratification. The proportion of arteries composing the 3 most tortuous vessels of preplus regression was similar to that of eyes that never developed ROP. Both groups had approximately the same percentage of arterioles as the 3 most tortuous vessels. The vessel type distribution of preplus progressed eyes was similar to that of arterioles as the 3 most tortuous vessels. The vessel type distribution of preplus progressed eyes was similar to that of arterioles as the 3 most tortuous vessels. In other words, as preplus progressed, arterioles became more tortuous than venules. For all 4 groups, venules were most of the 3 widest vessels. These quantitative findings validate clinical observations regarding the development and progression of plus disease.

In this small study, quantitative analysis identified group differences in width and tortuosity between eyes with preplus ROP that progressed spontaneously and eyes with preplus ROP that progressed to treatment. The areas under
the ROC curve, however, were not high. Thus, these data cannot be used at this juncture to predict the development of vision-threatening ROP in individual infants with high sensitivity and specificity. Owing to the possible disastrous visual consequences of untreated ROP, high sensitivity in the detection of severe ROP is arguably more important than is high specificity. Accordingly, computer-assisted analysis of digital images may be informative when used in concert with subjective clinical evaluation rather than when used for stand-alone screening. Quantitative criteria for preplus and plus ROP could be used as an adjunct to the current gold standard of clinical evaluation to reduce the number of unnecessary examinations in low-risk infants. Finally, software algorithms and digital imaging modalities are undergoing rapid advancements. Although this makes it difficult to compare results between published data, one can also be assured that quantitative analysis of ROP will only improve with updated iterations of digital cameras and image analysis software.

The subjective nature of the diagnosis of preplus and plus disease is a significant obstacle in the evaluation of ROP. Computer-assisted analysis of vascular changes in ROP has several potential advantages. In addition to increased reliability and accuracy, digital imaging analysis may be useful in telemedicine approaches to ROP screening. An objective classification system could be more easily applied to clinical research than is the subjective gold standard. Ultimately, quantitative analysis of vascular changes in ROP may improve the timely assessment and treatment of ROP and reduce lifelong consequences that may result from sight-threatening disease.

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Additional Contributions: This study was performed under a larger study examining digital imaging analysis software from the institutional review board at the Children’s Hospital of Philadelphia Protocol 4000.

REFERENCES