Vascular Dilation and Tortuosity in Plus Disease

Plus disease is the major factor in determining whether peripheral retinal ablation for retinopathy of prematurity is needed. Although the clinical definition of plus disease includes both dilation and tortuosity, previous reports have suggested that computer-based programs assessing tortuosity alone may be adequate to diagnose plus disease. The aim of this study was to determine the frequency of isolated dilation sufficient for plus disease (with insufficient tortuosity) and isolated plus-level tortuosity (with insufficient dilation) compared with the frequency of both plus-level dilation and plus-level tortuosity in a series of images.

Methods. In a previously published, institutional review board–approved study designed to compare the accuracy of computer-assisted image analysis using ROPtool with that of individual examiners, 6 pediatric ophthalmologists (S.F.F., Terri L. Young, MD, Laura B. Enyedi, MD, Graham E. Quinn, MD, Michael F. Chiang, MD, MA, and David K. Coats, MD) evaluated RetCam photographs of 190 different eyes from 117 premature infants. Of these photographs, 10 were excluded because of inadequate image quality as determined by one of us (D.K.W.) and 110 were excluded because they were determined to be without either dilation or tortuosity sufficient for plus disease by all of the experts. Therefore, a total of 70 images of 70 different eyes were included. The ophthalmologists independently scored each quadrant of each image by grading dilation and tortuosity separately (8 total grades per eye) as plus, preplus, or normal.

These scores were used to generate eye-level data. An eye-level grade of dilation (or tortuosity) sufficient for plus disease was present if at least 2 of the 4 quadrants in a single eye had dilation (or tortuosity) sufficient for plus disease. These grades were used to determine whether eyes had plus disease (2 quadrants of plus dilation and tortuosity), dilation sufficient but tortuosity insufficient for plus disease, tortuosity sufficient but dilation insufficient for plus disease, or dilation and tortuosity insufficient for plus disease. Thus, the reference standard for plus disease was dilation and tortuosity in the same 2 quadrants, which was the same definition used to define plus disease in both the Early Treatment for Retinopathy of Prematurity and Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity clinical trials. The same guideline was used for preplus disease, which we defined as in our previous studies as at least 2 quadrants of preplus dilation and tortuosity or worse.

For each ophthalmologist, the specificity of using dilation and tortuosity alone to diagnose plus disease was calculated, with both dilation and tortuosity as the reference standard. Therefore, each individual rater using only dilation or tortuosity was compared against himself or herself using both dilation and tortuosity. In this way, it was determined how often dilation was sufficient but tortuosity was insufficient for plus disease and how often tortuosity was sufficient but dilation was insufficient for plus disease (Figure). Specificity was calculated by dividing the number of eyes classified as not having plus disease as determined by dilation or tortuosity alone by the true number of eyes without plus disease as determined by dilation and tortuosity together. The identical analysis was also performed for the preplus level of disease or worse including the 70 images that were used in the plus analysis and the 110 images without dilation or tortuosity that were excluded from the plus analysis.

Figure. Examples of RetCam photographs used for the study. A, Dilation sufficient but tortuosity insufficient for plus disease (image courtesy of Michael Chiang, MD, MA). B, Tortuosity sufficient but dilation insufficient for plus disease (image courtesy of PHOTO-ROP).
**Results.** For plus disease, the specificities when using dilation alone for each consecutive grader were 71%, 95%, 83%, 87%, 48%, and 87% (mean, 79%; median, 87%). In comparison, the specificities when using tortuosity alone for each consecutive grader were 87%, 93%, 63%, 97%, 81%, and 83% (mean, 85%; median, 85%). For preplus disease, the specificities when using dilation alone were 74%, 96%, 83%, 74%, 19%, and 70% (mean, 71%; median, 75%), and the specificities when using tortuosity alone were 96%, 88%, 87%, 95%, 97%, and 95% (mean, 93%; median, 96%). The Table provides pooled frequency counts for eye-level analyses. Sensitivities were not calculated because they all equaled 100% by definition, ie, of those eyes with plus disease, all had dilation and tortuosity sufficient for plus disease.

**Comment.** Although plus-level dilation and plus-level tortuosity usually appear together, it is not uncommon for eyes to exhibit dilation without tortuosity sufficient for plus disease or tortuosity without dilation sufficient for plus disease. Our data suggest that these scenarios occur with roughly equal frequency, so it is important to consider both dilation and tortuosity in plus disease. In addition, both dilation and tortuosity appear to be important in diagnosing preplus disease. Because we used quadrant-level grades to generate eye-level grades, a limitation of our study is that we cannot address the relative contribution of dilation and tortuosity to an examiner’s overall impression (or gestalt) of plus disease. Our specific image set and disease definition may have affected the calculated specificities; however, the overall finding of the importance of both dilation and tortuosity remains consistent regardless of the precise numbers. These results have implications for the development of computer programs aimed at measuring plus disease and reducing subjectivity of its diagnosis.

**Table. Pooled Frequency Counts for Eye-Level Analyses**

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<tbody>
<tr>
<td>Dilation sufficient</td>
<td>136</td>
<td>63</td>
<td>414</td>
<td>194</td>
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<td>Dilation insufficient</td>
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<td>221</td>
<td>0</td>
<td>472</td>
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<tr>
<td>Tortuosity sufficient</td>
<td>136</td>
<td>46</td>
<td>414</td>
<td>47</td>
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<tr>
<td>Tortuosity insufficient</td>
<td>0</td>
<td>238</td>
<td>0</td>
<td>619</td>
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*The columns of plus disease and not plus disease show the number of eyes with either dilation or tortuosity sufficient for plus disease compared with the number of eyes with actual plus disease when considering both dilation and tortuosity (70 eyes ¥ 6 examiners = 420 total for dilation [sufficient and insufficient combined] and tortuosity [sufficient and insufficient combined]). The columns of preplus disease and not preplus disease show data for preplus disease or worse (180 eyes ¥ 6 examiners = 1080 total for dilation [sufficient and insufficient combined] and tortuosity [sufficient and insufficient combined]).


**COMMENTS AND OPINIONS**

**Genomic Typing of Uveal Melanoma**

The controversy regarding uveal melanoma genetic prognostication deserves comment. Shields et al2 rightly encouraged early treatment of small melanomas because 27% of these show monosomy 3 and high metastatic potential. Treating all small melanomas causes excessive morbidity, but observation risks shortening life. Biopsy helps resolve this dilemma, justifying low rates of complication and inconclusive results.

Shields et al2 observed that tumor size is a poor predictor of metastasis. Cytogenetic tumor typing identifies high-risk patients meriting recruitment into trials of any promising adjuvant systemic therapies. Such studies would otherwise require impossibly large patient numbers.3

Tsai and O’Brien1 warned that patients’ quality of life is diminished by a poor prognosis. This is untrue. They express caution for the false sense of security provided by a good prognosis; however, metastasis is rare with disomy 3 melanoma, especially if multiple predictors are analyzed.5,7 Genetic prognostication reassures patients who must otherwise cope with an excessively pessimistic prognosis.5 Tsai and O’Brien advocate aggressive metastatic screening regardless of genetic prognostics, but this causes unnecessary radiation exposure and expense to patients with disomy 3 melanoma and low metastatic risk.7

Robertson commented on the low incidence of monosomy 3 in Shields and colleagues’ study.1 This correlates with tumor size, which was smaller than in previous studies.1 Robertson criticized early treatment of small monosomy 3 melanomas because in the Collaborative Ocular Melanoma Study, the 8-year mortality rate was only 4%.