letters in the higher-dose group and 1 letter in the lower-dose group.

At the visit 10±2 weeks after stopping the levodopa treatment, the mean change in visual acuity in the amblyopic eye from baseline was +5 (±4) letters in the lower-dose group and +4 (±5) letters in the higher-dose group.

Levodopa-carbidopa was not discontinued by any subject during the 9-week dosing regimen. Adverse events were reported for 8 of 16 subjects (29 events) in the lower-dose group and 11 of 17 subjects (26 events) in the higher-dose group (eTable 2). No adverse events were considered serious. Headaches were reported by 6 subjects; a cold, upper respiratory tract infection, and cough were reported by 6; rash was reported by 4; and nausea and vomiting were reported by 3.

Comment. We enrolled a small cohort to gain experience with the drug, define the treatment dose for a future trial, and develop study procedures. The results suggested that levodopa-carbidopa therapy for residual amblyopia in older children and teenagers is well tolerated and may improve visual acuity. There was a suggestion of partial regression of the improvement in visual acuity after treatment was discontinued. No serious adverse effects were noted. Headache and nausea were infrequent. Without a patching-only control group, no conclusions about the efficacy, safety, or frequency of adverse effects associated with this treatment can be made. A placebo-controlled trial is necessary to determine whether levodopa can successfully augment occlusion therapy in the treatment of amblyopia.

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Plus Disease in Retinopathy of Prematurity: Quantitative Analysis of Standard Published Photograph

Plus disease is defined as abnormality of the posterior retinal vessels in which the arterial tortuosity and venous dilation meet or exceed those of a standard photograph selected by expert consensus in the 1980s.3-4 This method has limitations, and studies have suggested that interexpert agreement in plus disease diagnosis is variable.5 Magnification of the standard photograph is larger than that of indirect ophthalmoscopy, and peripheral vessels are not visible in the narrow field of view. It is also unclear which vessels cli-


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nicians should focus on while evaluating tortuosity and dilation. This study seeks to quantify vascular characteristics of the standard photograph compared with expert interpretations of plus disease. Such data could help assess clinical applicability of the standard photograph and contribute to development of objective disease definitions based on quantitative principles.

Methods. Thirty-four wide-angle retinal images were interpreted by 22 retinopathy of prematurity experts for presence of plus disease. For each wide-angle image, a reference standard diagnosis (plus disease or not plus disease) was defined using majority vote among experts.

Vessels from wide-angle images and from the standard photograph were analyzed by a computer-based system to calculate the mean arterial tortuosity index (ATI) (length of vessel segment divided by length of straight line connecting vessel ends) and the venous diameter (VD) (area divided by length of vessel) among all vessels in each image as described previously. Because ATI is a ratio, it is independent of magnification and resolution. However, comparison of VD values among different images required adjustments for magnification differences. This was done by normalizing all optic disc diameters to 1015 µm based on prior literature.

Sensitivity and specificity of the computer-based system for detecting plus disease were plotted as a function of cutoff values of ATI and VD that were used to separate plus disease from not plus disease (Figure 1) based on this reference standard. For example, the number of missed cases of plus disease (ie, false-negatives) would be expected to increase as the cutoff value of ATI (or VD) increases; therefore, sensitivity decreases as ATI (or VD) increases.

Results. The mean ATI of the standard photograph was 1.15, which was significantly lower than the ATI in wide-angle images that were diagnosed as plus disease (mean, 1.26; P = .003) and not plus disease (mean, 1.19; P = .001). The mean VD of the standard photograph was 66.88 µm, which was significantly lower than both plus disease in wide-angle images (mean, 81.63 µm; P = .002) and not plus disease in wide-angle images (mean, 78.95 µm; P < .001).

If the standard photograph parameter values were used as the cutoff for plus disease, the mean ATI of 1.15 would result in 85% sensitivity and 38% specificity, while the mean VD of 66.88 µm would result in 85% sensitivity and 14% specificity (Figure 1).

Comment. Anecdotally, we feel that some experts regard the standard photograph as showing plus disease appearing more severe than their personal cutoffs for plus disease. This is inconsistent with findings from our study. We compared the standard photograph with representative examples from 34 wide-angle images. This confirmed that the ATI in the standard photograph did appear low and suggested that after adjusting for magnification, the VD appeared visually similar to that seen in several wide-angle images diagnosed as not plus disease by experts (Figure 2). Therefore, we feel a possible explanation is that magnification and field of view in the standard photograph may cause difficulty for ophthalmologists.

A study limitation is that it was often difficult to identify precise disc margins during image normalization (although a consensus was reached among us), and infants may have true differences in disc size. Also, tortuosity as defined in this study was a gross measure, and future research involving other metrics for calculating tortuosity may be warranted.

These findings suggest that using the standard photograph as the cutoff definition for plus disease results in high sensitivity and low specificity compared with expert diagnoses from an independent set of wide-angle images. In other words, arterial tortuosity and venous dilation in the standard photograph may be less severe than what experts are considering to be plus disease. This raises...
questions about whether the current published photograph requires modification to represent true expert opinion or whether strategies are required to recalibrate ophthalmologists to the standard photograph.

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Figure 2. Representative images demonstrating the spectrum of quantitative vascular characteristics in the study images. A, Arterial tortuosity index (ATI) of all analyzed arteries. Image I had a mean ATI of 1.09 and was classified as not plus disease by expert reference standard. Image II had a mean ATI of 1.15 and is the standard photograph. Image III had a mean ATI of 1.15 and was classified as not plus disease. Image IV had a mean ATI of 1.48 and was classified as plus disease. B, Venous diameter (VD) of all analyzed veins. Image I had a mean VD of 57 µm and was classified as not plus disease by expert reference standard. Image II had a mean VD of 67 µm and is the standard photograph. Image III had a mean VD of 79 µm and was classified as not plus disease. Image IV had a mean VD of 82 µm and was classified as plus disease.

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Additional Contributions: Earl Palmer, MD, provided a digital copy of the standard photograph.


2. International Committee for the Classification of Retinopathy of Prematu-
Nonorganic visual loss (NOVL), also known as functional visual loss, is visual loss in the absence of evidence of a causal organic abnormality. The diagnosis of NOVL often presents a challenge to the ophthalmologist; ensuring that one has not overlooked a treatable, organic disease can be a frustrating, expensive, and time-consuming process in the face of poor reporter reliability.

Automated perimetry is often inadequate in the analysis of nonorganic visual field loss (NOVL). Abnormalities in indices of reliability (false-positive and false-negative rates and percentage of fixation losses) may be present in both organic and nonorganic disease. Furthermore, informed malingerers are able to reproduce visual field abnormalities on automated perimetry that are suggestive of NOVFL have been described, including the spiral field, star-shaped field, and tubular field. However, prior studies report a success rate of less than 50% in demonstrating these types of fields using Goldmann kinetic perimetry. Here we describe a novel use of kinetic perimetry designed to efficiently demonstrate and document a target visual field consistent with nonorganic visual field constriction.

Methods. Study Population. Institutional review board approval was obtained from Baylor College of Medicine. Twenty-six consecutive patients (45 affected eyes) with NOVL were seen by a single neuro-ophthalmologist (R.F.) at the Baylor College of Medicine Eye Clinic during an 8-month period from August 1, 2004, to April 1, 2005. Patients with NOVL who did not have a visual field defect, did not show up for their scheduled appointment for kinetic perimetry, or either were unable to fixate or responded only at central fixation in that eye during kinetic perimetry were excluded from the study population. This number included 1 patient with bilateral NOVL who could not fixate in 1 eye.

Thus, our final study population included 32 affected eyes in 18 consecutive patients who met the following criteria: (1) had visual loss that was found to be greater than that demonstrated on examination; (2) had no evidence of organic disease on examination, neuro-imaging, and/or electrophysiological testing that could explain the visual loss; and (3) successfully completed kinetic perimetry.

A control group included 2 eyes of 2 healthy subjects with no history of ocular disease except refractive error and with normal ophthalmic examination results as well as 8 eyes of 8 patients with documented organic visual field loss (5 eyes with primary open-angle glaucoma and 3 eyes with nonarteritic anterior ischemic optic neuropathy) who had visual field defects previously documented on automated perimetry.

Repeated III4E Isopter Method for Kinetic Perimetry. Using a Goldmann kinetic perimeter, the III4e and then the V4e isopters were plotted in the typical manner in which the stimulus presented from the periphery and moved toward fixation sequentially along opposite meridians. The III4e isopter was repeated beginning at the threshold previously plotted for the III4e isopter and then slowly moved toward fixation. This method of kinetic perimetry was also performed for the control group.

Results. The patient with NOVFL typically did not respond to the second III4e isopter stimulus when it first appeared, despite having seen the same stimulus at that position previously. As a result, the field plotted with the second III4e isopter was more constricted than the field plotted with the first III4e isopter, effectively demonstrating a variable visual field in the form of a target pattern that was obviously not consistent with organic disease (Figure 1).

A target pattern was defined as a pattern in which all or nearly all plots formed using the repeated III4e isopter were located more centrally than the plots formed using the original III4e isopter (Figure 1). Patients in whom a visual field was documented with the first III4e isopter but who then only responded at fixation on repeating the III4e isopter were included as having a positive target pattern. In 1 patient with bilateral visual loss, 1 eye did not respond to any stimulus in the temporal hemifield such that it was equivocal whether a true target pattern was present. We did not consider this eye to demonstrate a target pattern during our analysis.

The study population included 5 men (28%) and 13 women (72%). Three patients (17%) had unilateral visual loss, whereas 15 patients (83%) had bilateral involvement. Half of the patients (9 patients) had isolated visual field defects, while the other half (9 patients) had combined visual acuity and visual field loss. Thirteen patients (72%) had a history of depression, fibromyalgia, and/or anxiety.

Twenty-nine eyes (91%) in the study population showed a target pattern. No eyes in the control group demonstrated a target pattern. In the control group, virtually identical visual fields were plotted with the first and second III4e isopters, with minimal variation attributable to response lag time (Figure 2A and B).