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Structural and Functional Progression in the Early Manifest Glaucoma Trial

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Purpose: To elucidate the temporal relationship between detection of glaucomatous optic disc progression, as assessed by fundus photography, and visual field progression.

Design: Prospective, randomized, longitudinal trial.

Participants: Three hundred six study eyes with manifest glaucoma with field loss and 192 fellow eyes without any field defect at the start of the trial, from a total of 249 subjects included in the Early Manifest Glaucoma Trial (EMGT), were assessed.

Methods: Evaluation of visual field progression and optic disc progression during an 8-year follow-up period. Three graders independently assessed optic disc progression in optic disc photographs. Visual field progression was assessed using glaucoma change probability maps and the EMGT progression criterion.

Main Outcome Measures: Time to detection of visual field progression and optic disc progression.

Results: Among study eyes with manifest glaucoma, progression was detected in the visual field first in 163 eyes (52%) and in the optic disc first in 39 eyes (12%); in 1 eye (0%), it was found simultaneously with both methods. Among fellow eyes with normal fields, progression was detected in the visual field first in 28 eyes (15%) and in the optic disc first in 34 eyes (18%); in 1 eye (1%), it occurred simultaneously.

Conclusions: In eyes with manifest glaucoma, progression in the visual field was detected first more than 4 times as often as progression in the optic disc. Among fellow eyes without visual field loss at baseline, progression was detected first as frequently in the optic disc as in the visual field. *Ophthalmology 2016;123:1173-1180 © 2016 by the American Academy of Ophthalmology.*

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Glaucomatous progression can be observed as increasing functional loss in a series of visual fields or as increasing structural change in the optic nerve head or in the retinal nerve fiber layer. The relationship between structural and functional findings has been the object of many scientific studies.[1–13] A common, but not unanimous, contemporary opinion is that glaucomatous structural changes are detected more commonly early in the disease, whereas functional progression is seen more commonly at later stages of the disease, although there is variation among patients as to which of the two appears first.[14–17] This temporal relationship is relevant to be able to make appropriate decisions regarding when and how to use available instrumentation for diagnosis or regarding how to decide when to treat or to change treatment in patients during different stages of the disease.

In the Early Manifest Glaucoma Trial (EMGT), glaucoma patients were followed up using computerized perimetry and optic disc photography over long periods; the present analysis included prospective data collected over a period of up to 11 years. Thus, the EMGT offers an unusual opportunity to study the temporal relationship between structural and functional findings using regular fundus photography and visual field testing throughout the study. The aim of the present study was to elucidate the temporal relationship between optic disc progression and visual field progression among patients in the EMGT and to compare the results obtained in study eyes that had visual field defects at the beginning of the trial and fellow eyes lacking such loss at study inception.

Methods

As detailed in previous reports,[18] the EMGT (ClinicalTrials.gov identifier, NTC00000132; date of registration, September 23, 1999) included 255 glaucoma patients 50 to 79 years of age at the time of study enrollment. Patients included in the study mainly were recruited from a large population-based screening and were randomized equally either to treatment with argon laser trabeculoplasty plus betaxolol 5 mg/ml twice daily (Betoptic; Alcon, Fort Worth, TX) or to no treatment until progression was observed. Participants were followed up every 3 months for the first 4 years. Thereafter, some of the patients were seen every 6 months, but the vast majority continued follow-up at 3-month intervals. The study was conducted according to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Lund, Sweden, and also by the Committee on Research Involving Human Subjects of the State University of New York at Stony Brook. All patients provided informed consent.

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Eligibility criteria for inclusion in the EMGT included the presence of reproducible glaucomatous visual field defects as determined by the glaucoma hemifield test of the Humphrey perimeter (Carl Zeiss Meditec, Dublin, CA). Monoscopic fundus photographs were obtained at baseline and at the 3- and 6-month visits, and every 6 months thereafter.

Visual fields were assessed at each study visit. The EMGT criterion for visual field progression was applied[18]; that is, progression was determined to be definite only if 3 or more of the same test locations showed statistically significant progression in 3 consecutive visual fields compared with baseline. The method of assessment was glaucoma change probability maps.[19] The date of the last of the 3 visual field assessments showing progression was defined as the date of progression. All patients showing visual field progression were evaluated subsequently to rule out alternative explanations for the observed progression. Also, if the 3 or more test locations did not indicate change in the subsequent visual fields, it was not considered true progression.

We evaluated all disc photographs that had been obtained between the time of each patient's first 3-month visit and the year 2005, when our camera technique changed. All evaluated photographs were obtained through a dilated pupil using a modified 300 Zeiss fundus camera (Carl Zeiss, Oberkochen, Germany) and Kodachrome 64 film (Eastman Kodak, Rochester, NY). Baseline images were defined to be the photographs obtained at the 3-month visit, rather than those of the prerandomization baseline visit, to avoid inclusion of any possible immediate changes in optic disc configuration caused by the introduction of pressure-lowering treatment.[20,21] Photographs obtained with the new camera technique used after 2005 were not evaluated because this would have prevented masking of the temporal order of the images.

All studied photographs were digitized, and 3 disc readers, 2 who were experienced (A.H., B.B.) and 1 who was trained more recently (H.M.O.), independently evaluated each optic disc while masked to the temporal order and to all other patient data. The experienced readers are senior scientists with long experience in optic disc interpretation, including teaching and performing longitudinal studies on optic disc topography and comparisons with perimetric data.[22,23] The more recently trained reader is a resident who had been working with this study for 2 years together with the senior authors. During this period, the more recently trained reader had frequent opportunity to work with optic disc reading together with one or both of the senior authors. At an early stage, the more recently trained reader went through an Internet-based training course for the appraisal of optic disc progression before assessment of the eyes in the study.[24] High-quality computer screens were used in the assessment, allowing disc readers the ability to magnify photographs to the desired size. Progression was recognized mainly as changes in the course of small vessels on the optic disc surface. Increasing pallor, peripapillary atrophy, or optic disc hemorrhages were not considered proof of optic disc progression. A random sample of optic discs thus determined to have progressed is presented in Figure 1 (available at www.aaojournal.org).

Photographic evaluation was carried out in the following order. First, we looked for progression in pairs of fundus photographs, in which 1 photograph came from the 3-month visit and the second photograph was the last available photograph of reasonable quality. The 2 photographs were masked as to temporal order and presented for evaluation in randomized order, with study eyes and fellow eyes intermingled. One-fifth of the evaluated photograph pairs were control pairs in which 2 separate fundus photographs of study eyes obtained on the same date were used. Then, one disc reader (H.M.O.) studied all full sequences of photographs of all eyes to rule out that any optic disc progression had been missed in the pair analysis.

If an eye was judged to have progressed and the temporal order was determined correctly, we evaluated the entire series of that patient's photographs sorted in chronological order, and the date of the first photograph where progression could be seen was recorded. Progression had to be sustainable throughout the series unless the earliest photograph showing progression also was the one that originally had shown progression in the first step. Any disagreement among readers was settled through consensus, both regarding the existence of progression and the date of progression.

The same 3 disc readers evaluated the 3-month photographs of fellow eyes to assess whether the optic nerves were glaucomatous. Fundus photographs from study-eligible glaucoma eyes were mixed randomly with fellow eyes. These eyes were classified as having preperimetric glaucoma when an optic disc hemorrhage was present or the disc showed convincing signs of glaucomatous damage, for example, a clear notch or increased excavation and rim thinning. In further analyses, fellow eyes were divided in 3 groups: (1) eyes with normal intraocular pressure and no signs of glaucoma in their optic discs or visual fields, (2) eyes with ocular hypertension, and (3) eyes designated as having preperimetric glaucoma because of abnormal optic discs or disc hemorrhages.

To compute interrater agreement among the disc readers, Cohen's κ values and prevalence-adjusted, bias-adjusted κ values were calculated.[25] The arithmetic mean was used for both measures of interrater agreement.[26,27] Cumulative incidence functions were calculated for the competing events: visual field progression first, optic disc progression first, and death occurring within 6 months from the last available follow-up in patients without progression.[28] Some patients had both eyes included as study eyes. To determine 95% confidence intervals (CIs) for the various cumulative incidences at 96 months (median follow-up time), a bootstrap technique was used with 1000 repetitions and patient as a cluster.[29] The conditional probability for visual field progression or optic disc progression to occur first, given that a progression has occurred, was calculated with 95% CIs. For study eyes, robust 95% CIs were determined with the patient as the cluster variable.[30] Statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp, Armonk, NY) and Stata software version 14 (StataCorp, College Station, TX).

Results

The 255 glaucoma patients included in the EMGT had a median age of 68 years at baseline, and 66% were women. Twelve eyes of 6 patients were excluded because follow-up was too short to be able to reach progression according to the criteria used in the EMGT. That is, we were unable to include eyes having fewer than 2 fundus photographs obtained after baseline, having fewer than 3 visual fields obtained after baseline, or both.

Of the 498 eyes analyzed, 306 had manifest glaucoma and 192 eyes were defined as fellow eyes, that is, eyes without visual field defects at baseline. Of the 192 fellow eyes, 116 (60%) had seemingly normal discs and normal intraocular pressure, 39 (20%) were ocular hypertensive eyes (intraocular pressure >21 mmHg), and 37 (19%) were classified in the present analysis as having preperimetric glaucoma, 4 of those on the basis of an optic disc hemorrhage only.

Median follow-up time was 96 months (8 years), with a minimum of 9 months and a maximum of 132 months, for both study and fellow eyes. The median value of perimetric mean deviation at baseline was −4.0 dB for study eyes and −0.6 dB for fellow eyes.