Long-Term Follow-up in Preperimetric Open-Angle Glaucoma: Progression Rates and Associated Factors

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• PURPOSE: To investigate the rate of progressive visual field (VF) loss and associated factors for structural or functional progression in preperimetric open-angle glaucoma (OAG).

• DESIGN: Longitudinal, observational study.

• METHODS: We included 127 eyes of 127 preperimetric OAG patients who were treated with topical medication and followed for more than 5 years. All patients underwent stereo optic disc photography, red-free retinal nerve fiber layer (RNFL) photography, frequency doubling technology perimetry, and standard automated perimetry (SAP). Progression was defined as a structural (glaucomatous change confirmed by stereo optic disc and red-free RNFL photography) or functional (new glaucomatous defect on SAP) deterioration. The progression rate of SAP mean deviation (dB/year) and factors associated with progression were evaluated.

• RESULTS: Glaucoma progression was detected in 72 of 127 eyes (56.7%). Mean rate of VF progression was −0.39 ± 0.64 dB/year in all patients; −0.66 ± 0.60 dB/year in progressors and −0.03 ± 0.24 dB/year in nonprogressors. A multivariate Cox proportional hazard model revealed that optic disc hemorrhage (hazard ratio [HR] = 1.718, P = .031) and the percentage reduction in intraocular pressure (IOP; HR = 0.964, P = .002) were significantly associated with disease progression. Patients with disc hemorrhage had a greater cumulative probability of progression than those without disc hemorrhage (P = .014 by log-rank test).

• CONCLUSIONS: Our results support the importance of lowering IOP, even at the preperimetric stage. Preperimetric glaucoma patients with disc hemorrhage and insufficient IOP control should be carefully monitored for greater risk of progression. (Am J Ophthalmol 2015;159:160–168. © 2015 by Elsevier Inc. All rights reserved.)

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PREPERIMETRIC GLAUCOMA IS DEFINED AS THE PRESence of characteristic glaucomatous optic disc and nerve fiber layer damage in the absence of visual field (VF) defects on conventional achromatic automated perimetry. Since functional damage is not apparent in preperimetric glaucoma, the decision to initiate therapy needs to be determined on an individual basis, considering each patient's benefit-to-risk ratio.

Previous studies have supported the protective role of lowering intraocular pressure (IOP) in glaucoma patients with a wide spectrum of disease severity. The Ocular Hypertension Treatment Study demonstrated that the cumulative probability of developing glaucoma was reduced by 60% in the medication group compared to the observation group.[1] The Early Manifest Glaucoma Trial also showed considerable beneficial effects of treatment, including significantly delayed glaucoma progression.[2,3] The Collaborative Normal-Tension Glaucoma Study reported that lowering IOP reduces clinically manifested glaucoma progression from 27% to 12%.[4] The Advanced Glaucoma Intervention Study also reported the association between maintaining IOP less than 18 mm Hg and reduced VF defects progression.[5]

Based on these studies, IOP reduction is expected to preserve vision, even in preperimetric glaucoma patients. However, less is known about the extent of the benefits of lowering IOP in preperimetric open-angle glaucoma (OAG) patients. Additionally, our knowledge of factors associated with progression in these patients is limited. In this regard, identifying progression rates and treatment outcome in preperimetric glaucoma would give clinicians a basis for when to initiate IOP-lowering treatments in these patients.

The purpose of our study was to investigate the rate of VF changes over the long term (at least 5 years) in preperimetric OAG patients undergoing treatment. In addition, potential systemic and ocular characteristics were compared between progressors and nonprogressors to identify factors associated with structural or functional glaucoma progression.

METHODS

PATIENTS WHO HAD BEEN NEWLY DIAGNOSED WITH preperimetric OAG at the Glaucoma Clinic of Seoul

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National University Hospital between January 2005 and December 2007 were consecutively included in this retrospective observational cohort. All patients were followed for at least 5 years after the initial visit. Study conduct adhered to the tenets of the Declaration of Helsinki and the study protocol was approved by the institutional review board of Seoul National University Hospital.

Inclusion criteria were: (1) preperimetric OAG diagnosis in 1 or both eyes at the first clinic visit, (2) no history of IOP-lowering treatment use, (3) attended follow-up visits every 6 months for at least 5 years, and (4) treated with only topical medications during the follow-up period. In addition, patients had to have a best-corrected visual acuity better than 20/40, a spherical equivalent within ±5.0 diopters, a cylindrical correction of less than 3.0 diopters, an open anterior chamber angle at the initial examination, good-quality stereo optic disc photography and red-free retinal nerve fiber layer (RNFL) photography images, and reliable VF testing results (fixation loss <20%, false-positive errors <15%, and false-negative errors <15%). For cases in which both eyes met all eligibility criteria, 1 eye was randomly chosen as the study eye before analyses. Patients were excluded if any of the following were present: manifest glaucoma, optic neuropathy, history of ocular surgery (other than uncomplicated cataract surgery), or any other systemic or ocular pathology known to affect the optic disc, RNFL, or VF (eg, retinal vascular occlusive disease, diabetic retinopathy, hypertensive retinopathy, uveitis).

All patients underwent full ophthalmic examinations, including measurement of best-corrected visual acuity and spherical equivalent by autorefractor (KR-890; Topcon Corporation, Tokyo, Japan). A slit-lamp examination, anterior chamber angle gonioscopy, dilated fundus examination, and corneal pachymetry (Pocket II Pachymeter Echo graph; Quantel Medical, Clermont-Ferrand, France) were also performed. A Goldmann applanation tonometer was used to measure IOP at baseline (prior to beginning topical therapies) and at every follow-up visit. For baseline IOP, the average of diurnal IOP measured at 8:30 AM, 10:00 AM, 11:30 AM, 1:00 PM, 2:30 PM, and 4:00 PM was used. At the baseline examination, all patients were also evaluated with color stereo optic disc photography, red-free RNFL photography (Vx-10; Kowa Optimed, Tokyo, Japan), frequency doubling technology (FDT) perimetry (Matrix Frequency Doubling Perimeter; Carl Zeiss Meditec Inc, Dublin, California, USA), and standard automated perimetry (SAP; 30-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec Inc). All patients attended regular follow-up visits 6 months apart, at which time patients underwent clinical examination, stereo disc photography, red-free RNFL photography, and SAP. All patients were treated for glaucoma at the discretion of the attending ophthalmologist (D.M.K.), who aimed to reduce baseline IOP by at least 20%. When this was not accomplished, further treatment decisions were made by the treating physician.

The preperimetric OAG diagnosis was given to patients with a glaucomatous optic disc appearance (eg, neuroretinal rim thinning, notching, excavation) and/or RNFL defects, as confirmed on stereo disc and RNFL photography.[6] All disc and RNFL photography images were evaluated by 2 glaucoma specialists (K.E.K., J.W.J.) in a masked fashion. Discrepancies between observers were resolved by consensus or adjudication by a third glaucoma specialist (D.M.K). Patients should have a normal VF on conventional SAP at the initial examination, regardless of the presence or absence of baseline FDT perimetry abnormalities. Baseline FDT perimetry and SAP were performed within 2 weeks of each other. Normal FDT perimetry and SAP results were defined as mean deviation (MD) and pattern standard deviation (PSD) within the 95% confidence limits and a glaucoma hemifield test result within normal limits. Glaucomatous defects in FDT perimetry were defined as a cluster of 2 or more points in the pattern deviation probability plot with $P < 5\%$, a PSD of $P < 5\%$, or a glaucoma hemifield test result outside normal limits.[7]

• **DETERMINATION OF GLAUCOMA PROGRESSION:** Color stereo disc photography, red-free RNFL photography, and SAP were performed and assessed at each regular follow-up visit. Structural changes on disc and RNFL photography and functional changes on SAP determined the patient's progression status, as described below. The time at which structural and/or functional deterioration was first confirmed by stereo disc photography, red-free RNFL photography, or SAP was defined as the progression endpoint.

Progressive optic disc changes (ie, focal or diffuse narrowing, neuroretinal rim notching, increased cup-to-disc ratio, adjacent vasculature position shift) were determined by comparing serial stereo disc photography images and were regarded as glaucomatous progression. Changes in an RNFL defect (determined with serial RNFL photography), defined as the appearance of a new defect or an increase in width or depth of an existing defect, were regarded as structural progression.[8] Two observers (K.E.K., J.W.J.), who were masked to all other patient information, independently evaluated all photographs. Each patient was classified as a structural nonprogressor or progressor based on disc and RNFL photography image interpretation. In cases of disagreement, a third glaucoma specialist (D.M.K.) served as an adjudicator.

Patients were classified as having functional progression if new and reproducible glaucomatous VF defects, corresponding to structural damage, were found on SAP. A glaucomatous VF defect was defined as (1) presence of 3 or more non-edge points with a probability of being normal of $P < 5\%$, and 1 of these points having a pattern deviation of $P < 1\%$; (2) a PSD of $P < 5\%$; or (3) a glaucoma hemifield test result outside normal limits. Visual field tests were repeated within a month to confirm functional progression