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Glaucoma Structural and Functional Progression in American and Korean Cohorts

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Purpose: To compare the rate of glaucoma structural and functional progression in American and Korean cohorts.

Design: Retrospective longitudinal study.

Participants: Three hundred thirteen eyes from 189 glaucoma and glaucoma suspects, followed up for an average of 38 months.

Methods: All subjects were examined semiannually with visual field (VF) testing and spectral-domain optical coherence tomography. All subjects had 5 or more reliable visits.

Main Outcome Measurements: The rates of change of retinal nerve fiber layer (RNFL) thickness, cup-to-disc (C/D) ratios, and VF mean deviation (MD) were compared between the cohorts. Variables affecting the rate of change for each parameter were determined, including ethnicity, refraction, baseline age and disease severity, disease subtype (high- vs. normal-tension glaucoma), clinical diagnosis (glaucoma vs. glaucoma suspect), and the interactions between variables.

Results: The Korean cohort predominantly demonstrated normal-tension glaucoma, whereas the American cohort predominantly demonstrated high-tension glaucoma. Cohorts had similar VF parameters at baseline, but the Korean eyes had significantly thinner mean RNFL and larger cups. Korean glaucoma eyes showed a faster thinning of mean RNFL (mean, −0.71 μm/year vs. −0.24 μm/year; $P < 0.01$). There were no detectable differences in the rate of change between the glaucoma cohorts for C/D ratios and VF MD and for all parameters in glaucoma suspect eyes. Different combinations of the tested variables significantly impacted the rate of change.

Conclusions: Ethnicity, baseline disease severity, disease subtype, and clinical diagnosis should be considered when comparing glaucoma progression studies. *Ophthalmology 2016;■:1–6 © 2016 by the American Academy of Ophthalmology.*

Glaucoma is a multifactorial optic neuropathy characterized by the progressive loss of retinal ganglion cells and optic nerve damage associated with visual field (VF) defect. Determining the rate of glaucomatous changes over time has an important impact on the management of patients and dictates clinical intervention. The introduction of ocular imaging into the routine clinical management of glaucoma subjects allows for the detection of micron-scale structural changes, and it has ignited widespread interest in glaucoma progression detection. Although these studies provide important insight into the disease mechanisms and clinical detection, the effect of the diversity of the populations participating in these studies has not been considered thoroughly. Ethnicity, refractive error, disease subtype prevalence, treatment approach, and other variables may have an important effect on glaucomatous rate of change, thus putting into question the generality of the reported information. For example, high-tension glaucoma (HTG) has been reported to be most prevalent in black and white persons, whereas normal-tension glaucoma is prevalent in east Asian persons.[1,2] Furthermore, black persons tend to have more aggressive glaucoma compared with white persons.[3–5] It has been reported that variability in progression rates also has been related to age groups and disease types.[6–8] However, a rigorous comparison between cohorts with similar baseline characteristics, but different population compositions, has not been performed to assess the effect on the progression rate and to determine which variables impact the rate. We hypothesized that the composition of the participating populations in longitudinal glaucoma studies has a significant effect on the rate of structural and functional progression. The purpose of this longitudinal study was to compare glaucoma structural and functional rates of change in 2 similar cohorts enrolled in discrete geographical locations that differ significantly in ethnic composition and type of glaucoma.

Methods

Subjects

Glaucoma subjects and glaucoma suspects from the Pittsburgh Imaging Technology Trial and the glaucoma clinic of the Asan Medical Center, Seoul, Korea, were included in the study. The

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Pittsburgh Imaging Technology Trial is an ongoing prospective, longitudinal study designed to assess ocular structure over time carried out at the University of Pittsburgh Medical Center Eye Center. Consecutive subjects who qualified for the study were enrolled at both sites. The institutional review boards and ethics committees of both institutions approved this study. This study followed the tenets of the Declaration of Helsinki and was conducted in compliance with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all subjects.

Study Protocol

All participants underwent full comprehensive ocular examinations, including a review of medical history, measurement of best-corrected visual acuity, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, VF testing (Humphrey Field Analyzer; Zeiss, Dublin, CA), and spectral-domain optical coherence tomography (Cirrus HD-OCT; Zeiss) at baseline and every 6 months afterward, unless otherwise medically indicated. Subjects were 40 years of age or older, had a visual acuity of 20/60 or better, had a spherical equivalent refractive error of between −6.00 and +6.00 diopters (D), and had 5 or more visits with reliable testing results. Subjects were excluded from the study if they had a history of diabetes, had any macular pathologic features, had any conditions affecting VF and retinal thickness other than glaucoma, had a history of ocular trauma or surgery other than uncomplicated glaucoma interventions, or had undergone cataract extraction. Additionally, subjects were excluded for the use of any medication known to affect the retina. Both eyes were included in the study if they were eligible. For subjects who underwent a cataract extraction surgery, their refraction was recorded from the visits before the surgery.

Clinical Diagnosis

Eyes were defined as having HTG if there was a glaucomatous VF defect at baseline, records of intraocular pressure of more than 21 mmHg and optic nerve head (ONH) cupping of more than 0.6, or the clinical detection of a retinal nerve fiber layer (RNFL) defect. Normal-tension glaucoma (NTG) eyes were included if they exhibited the same optic disc and VF criteria as the HTG patients, with the exception that their intraocular pressure was 21 mmHg or less at any time point.

Glaucoma suspect eyes were defined as those with an intraocular pressure of 22 to 30 mmHg, asymmetric ONH cupping (difference in vertical cup-to-disc [C/D] ratio of more than 0.2 between eyes), abnormal appearance of the ONH as described above, or the contralateral eye of unilateral glaucoma, all in the presence of normal VF results. Glaucoma suspects had no history of retinal pathologic features, laser therapy, or intraocular surgery.

Visual Field Testing

All subjects underwent Swedish interactive thresholding algorithm 24-2 perimetry (SITA standard; Humphrey Field Analyzer; Zeiss) testing. Qualified VF examinations had less than 30% fixation losses, false-positive responses, or false-negative responses. Mean deviation (MD) was used for the analysis.

Spectral-Domain Optical Coherence Tomography

All subjects underwent spectral-domain optical coherence tomography using the Optic Disc Cube 200 × 200 scan protocol to obtain the circumpapillary RNFL thickness measurements. Scans with signal strength of less than 7, motion artifacts (assessed subjectively as a medium vessel diameter discontinuity of blood vessels), or scans with segmentation errors were excluded. Mean RNFL and 2 ONH parameters (average and vertical C/D ratio) were used in the analysis.

Definition of Progression

Structural progression, as detected by OCT, was defined by 2 independent methods. Guided progression analysis (GPA) was provided by the device's commercial software. Likely and possible progression were considered as progression when detected in the RNFL thickness map, RNFL profile average RNFL thickness, or average C/D ratio progression analyses. In the linear mixed effects (LME) analysis, a statistically significant negative slope ($P<0.05$) computed by the LME model while accounting for baseline age was considered progression.

Functional (VF) progression was determined by the event analysis of the GPA report, with likely and possible progression considered as progression when these designations appeared in the final visit. The trend analysis was determined for the VF MD by computing the rate of change using an LME model. A statistically significant negative slope was considered to be progression.

Statistical Analysis

Baseline characteristics were compared between Korean and American cohorts using generalized estimating equations to take into account the correlations between both eyes of a given subject. To determine the rates of change over time of analyzed parameters, LME models accounting for baseline age were used. To determine what variables impacted the rate of change of the investigated parameters in the entire population, an analysis of covariance model accounting for ethnicity, refraction (reported as spherical equivalent), baseline age and disease severity (as reflected by the baseline level of the individual tested parameter), disease subtype (HTG or NTG), clinical diagnosis (glaucoma or glaucoma suspect), and the interactions between these potential confounders was used. A P value less than 0.05 was considered to be statistically significant. R Language and Environment for Statistical Computing program (version 3.1.1; R Development Core Team. R: A Language and Environment for Statistical Computing. R Found Stat Comput; 2008) with geepack and lme4 packages was used for the statistical analysis.[9]

Results

The characteristics of the study population are summarized in Table 1. The American cohort included 81 glaucoma and 45 glaucoma suspect eyes from 69 subjects; the Korean cohort included 91 glaucoma and 96 glaucoma suspect eyes from 120 subjects. The American cohort included white (84%) and black (16%) persons with HTG (96%), whereas the Korean cohort included subjects with exclusively Korean origin and predominantly NTG (87%). At baseline, the Korean cohort was significantly younger than the American cohort, with thicker RNFL and larger C/D ratio measurements. There was no difference in VF MD and refractive error (reported as the spherical equivalent) between the cohorts. The mean length of follow-up in the American cohort was 37.5 months with a mean of 7 visits per eye (range, 5−14 visits). In the Korean cohort, the mean follow-up was 37.7 months with a mean of 6 visits per eye (range, 5−8 visits). There was no difference in follow-up duration between the 2 cohorts.