의학석사 학위논문

Association of Inter-Eye Visual Field Asymmetry with Progression of Primary Open-Angle Glaucoma

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ABSTRACT

Association of Inter-Eye Visual Field Asymmetry with Progression of Primary Open-Angle Glaucoma

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Purpose: To investigate the relationship between inter-eye visual field defect (VFD) asymmetry and subsequent visual field (VF) progression in primary open-angle glaucoma (POAG).

Methods: One hundred and twenty-two (122) eyes of moderate-stage POAG eyes (61 patients) with a single-hemifield defect were followed over 5 years. Participants were categorized into three groups based on the initial VF pattern: (1) unilateral VFD, (2) bilateral VFD within the same hemifield (superior-superior, inferior-inferior), (3) bilateral VFD within the opposite hemifield (superior-inferior). The mean deviation (MD) difference between the inter-eye was defined as the inter-eye mean deviation asymmetry index (iMAI). The inter-eye hemifield MD difference within the same hemifield was calculated as the inter-eye

hemifield visual-sensitivity asymmetry index (ihVAI). Global VF progression and MD slope were evaluated, and factors associated with glaucoma progression were assessed.

Results: During the 7.6 ± 2.4 year follow-up period, progression was detected in 14 of 21 unilateral VFD eyes (66.7%), 7 of 20 bilateral VFD eyes within the opposite VF hemifield (35.0%), and 4 of 20 bilateral VFD eyes within the same VF hemifield (20.0%) (P=0.007). There was statistically significant cumulative probability of progression greater in unilateral VFD eyes (55%) with a steeper MD slope (P=0.001). A faster MD slope was associated with greater iMAI (P<0.025). Disc hemorrhage (P=0.049), greater iMAI (P=0.011), and greater ihVAI (P=0.007) were significant factors for glaucoma progression.

Conclusions: Among POAG eyes with comparable hemifield VFDs, eyes without corresponding-hemifield defect in the fellow eye showed faster rates of progression compared to those with corresponding-hemifield defect.

Keywords: Glaucoma; Primary open-angle; Visual field; Hemifield defect; Asymmetric; Progression; Rate of change; Risk factor

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Chapter 1. Introduction

Glaucoma is the leading cause of irreversible blindness worldwide, affecting nearly 70 million people. The global prevalence is approximately 3.05% for the population aged 40 to 80 years old.[1, 2] Glaucoma progression is not uncommon, and despite treatment, most patients still progress. At 20 years' follow-up, the Kaplan-Meier cumulative probability of glaucoma-related blindness in at least one eye has been estimated to be 27%, and for both eyes, 9%.[3]

Well-known risk factors for primary open-angle glaucoma (POAG) include older age, elevated intraocular pressure (IOP),[4] ethnic background, positive family history for glaucoma, large IOP fluctuation, thinner central corneal thickness (CCT), and disc hemorrhage (DH).[4-12] More knowledge in this field will help the clinician to identify patients who require more care and/or more aggressive treatment to achieve a better outcome.

POAG generally affects both eyes, but often presents asymmetrically with asymmetric visual field defect (VFD).[13-15] Previous studies have documented inter-eye asymmetry and its relationship with intraocular factors such as IOP, myopia, optic nerve head (ONH) parameters, retinal nerve fiber layer (RNFL) thickness, and inter-eye vessel density asymmetry.[14, 16-20] Also, inter-eye IOP asymmetry and visual field (VF) asymmetry has been reported to increase the risk of POAG development in ocular hypertension patients.[21] However, to our knowledge, studies based on the inter-eye asymmetry of VFD and its relation to glaucoma progression are limited.

In this longitudinal study, we compared the rate of disease progression in POAG patients with inter-eye asymmetric and symmetric VFD. That is, determined whether glaucoma progression in POAG eyes is affected by the condition of the fellow eye. In addition, we presented a novel

index of asymmetric VFD and focused on uncovering the risk factors of POAG progression.

Chapter 2. Methods

This was a retrospective, longitudinal cohort study designed to evaluate the visual function of glaucoma. The data was retrieved from the clinical data warehouse of Seoul National University Hospital Patients Research Environment (SUPREME) based on a medical records review. This study was approved by the Seoul National University Hospital Institutional Review Board, and informed consent was waived due to the study's retrospective nature. All of the investigations and procedures adhered to the tenets of the Declaration of Helsinki.

2.1. Study Participants

Subjects who had been diagnosed with POAG at the Glaucoma Clinic of Seoul National University Hospital from January 2008 to June 2018 and been followed up regularly at a 6-month interval for a minimum of 5 years were enrolled.

The main inclusion criteria were moderate-stage POAG (mean deviation [MD] between −12 dB and −6 dB) with a single-hemifield defect. Additionally, the patients had a best-corrected visual acuity (BCVA) better than 20/30, a spherical equivalent refractive error between -6.00 and +3.00 diopters, and reliable VF testing results (fixation loss <20%, false positive errors <15%, and false-negative errors <15%).

POAG was defined as the presence of glaucomatous optic disc with typical glaucomatous visual field damage on standard automated perimetry (SAP) at three initial consecutive VF examinations, and an open angle. IOP was not considered in the determination of patient eligibility for the POAG group. Glaucomatous VF change was defined as (1) glaucoma hemifield test (GHT) values outside the normal limits or (2) three or more abnormal contiguous points with a probability of

$P < 0.05$, of which at least one point has a probability of $P < 0.01$ on a pattern deviation (PD) plot, or (3) a pattern standard deviation of $P < 0.05$. Determination of glaucoma severity was based on baseline MD measurements using the Hodapp–Parrish–Anderson grading scale.[22] The criteria for single–hemifield defect were based on the previous literature[23–25]: (1) VFD with a sharp border along the horizontal meridian and (2) both nasal and temporal involvement. Normal VFs were required to have consistently normal and reliable VF results from at least > 2 SAP tests. In addition, they could not have any test points with a probability level less than 2% and no clusters of ≥ 3 adjacent points with a probability of less than 5% on the PD probability plots.[26] The first 1 to 2 VF results were excluded so as to minimize learning effects, and unreliable results also were excluded. For tests showing unreliable results or suspected progression, clinicians were allowed to check the test more frequently, and more than 5 reliable VF tests at separate visits were required for analysis. All of the subjects received treatment consisting of medication, laser trabeculoplasty, or any combination thereof. The better eye and worse eye were defined based on the baseline MD values. The worse eye, which is to say, the eye with the lower MD value, was selected as the study eye for further analysis.

Subjects were excluded for the following reasons: secondary open–angle glaucoma (i.e. steroid–induced glaucoma); evidence of pseudoexfoliation or pigment dispersion syndrome; ocular surgery history such as cataract surgery, glaucoma surgery or vitrectomy possibly affecting the VF test; history of strabismus; history of uveitis, trauma, or inflammatory disease; any retinal or neurologic disease possibly affecting the VF examination results.

All of the patients were reviewed for demographic and systemic factors including history of diabetes mellitus and systemic hypertension, and all

had undergone a complete ophthalmic examination including visual acuity assessment, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland), gonioscopy, dilated fundus exam, digital color disc photography, red-free RNFL photography (TRC-50IX; Topcon Corporation, Tokyo, Japan), CCT measurement (Orbscan 73 II, Bausch & Lomb Surgical, Rochester, NY, USA), axial length measurement (Axis II PR; Quantel Medical, Inc., Bozeman, MT, USA), Cirrus spectral-domain optic coherence tomography (SD-OCT; Carl Zeiss Meditec, Dublin, CA, USA), as well as SAP 30-2 testing (Humphrey Field Analyzer [HFA]; Carl Zeiss Meditec, Dublin, CA, USA).

Baseline IOP was defined as the average IOP of two consecutive visits in the absence of IOP-lowering medication usage. The mean IOP was calculated as the average of IOPs taken at the respective visits during the observation period. IOP fluctuation was defined based on the standard deviation of those values. Disc and RNFL photography were taken after full dilation of the pupil (1% tropicamide, 2.5% phenylephrine). DH was defined as an isolated flame-shaped or splinter-like hemorrhage on the optic disc or in the parapapillary area extending to the border of the optic disc. Beta-zone (ß-zone) parapapillary atrophy (PPA) was characterized by marked atrophy of the retinal pigment epithelium and choriocapillaris, with good visibility of the sclera and large choroidal vessels.

2.2. Inter-Eye Visual Field Defect Pattern

Subjects were classified into 3 categories according to the inter-eye pattern of hemifield defect at baseline:
(1) Unilateral VFD: one superior- or inferior-hemifield defect in the study eye and normal VF results in the contralateral eye

(2) Bilateral VFD within the same hemifield: bi-superior or bi-inferior hemifield defect
(3) Bilateral VFD within the opposite hemifield: one-superior hemifield defect and contralateral-inferior hemifield defect

2.3. Inter-Eye Visual-Sensitivity Asymmetry Index

The inter-eye visual-sensitivity asymmetry index was determined based on the inter-eye VF exams: difference between the (1) overall MD and (2) hemifield mean deviation (HMD) values in the inter-eye mirrored GHT. The GHT, that is incorporated in the HFA, assigns a score to each test point based upon values presented in the PD probability maps and then calculates a sum for each sector. The pointwise HMD values in the concomitant hemifield (bi-superior or bi-inferior homonymous hemifield) were calculated as described elsewhere.[27]
The new indices were defined as the absolute values as follows:
(1: worse eye, 2: better or normal eye)
(a) Inter-eye MD Asymmetry Index (iMAI) = MD1 - MD2
(b) Inter-eye MD Asymmetry Ratio (iMAR) = (MD1 - MD2) / MD2
(c) Inter-eye hemifield Visual-sensitivity Asymmetry Index (ihVAI) = HMD1 - HMD2
(d) Inter-eye hemifield Visual-sensitivity Asymmetry Ratio (ihVAR) = (HMD1 - HMD2) / HMD2

2.4. Assessment of Glaucoma Progression

Glaucoma progression was defined as functional change on VF tests. Progression of VF was evaluated by two methods: (1) "event-based" analysis and (2) "trend-based" analysis. Event-based analysis using the Humphrey field analyser with guided progression analysis was used to determine progression, and only "likely progression" was considered to be VF progression. In the trend-based analysis, the rate of progression based on the change of MD against time was calculated. One glaucoma specialist reviewed all of the patients' VF results to ensure the absence of any artifactual results.

2.5. Statistical Analysis

The categorical data were analyzed by chi-square test, and continuous variables were compared with the t-test and ANOVA test results that had been corrected for multiple comparisons according to the Bonferroni method. To determine the inter-observer reproducibility, the intra-class correlation coefficient (ICC) with its confidence interval (CI) was calculated by two independent examiners. Linear regression analysis was used to calculate the rate of MD and to examine potential associations between the new indices and the VF progression rate. The intergroup cumulative risk ratios of functional progression were compared by Kaplan-Meier survival analysis and log rank test. The first time progression detection was found was regarded as the endpoint in survival analyses. The hazard ratios (HRs) of glaucoma progression were estimated with covariates using Cox proportional hazard modeling. The variables with significance at $P < 0.10$ were included in a multivariate model. The final multivariate model was developed by means of backward elimination, and the HRs with 95% CIs were calculated. Statistical analyses were performed using statistical software

(SPSS, version 22.0; SPSS Inc., Chicago, IL, USA). All of the P values were 2-sided and were considered statistically significant when less than 0.05.

Chapter 3. Results

Among the initial 74 POAG subjects, 13 were excluded from further analysis, 11 having undergone intraocular surgery (9 eyes, uncomplicated cataract surgery; 2 eyes, combined vitrectomy), and 2 having been diagnosed with combined retinal diseases during the course of the follow-up. Finally, a total of 61 subjects (122 eyes) were included in the study (mean age: 60.1 ± 12.2 years, range: 32-88 years; mean follow-up period: 7.6 ± 2.4 years).

3.1. Demographic and Clinical Characteristics

The demographics and clinical characteristics of the patients are summarized in Table 1, and an inter-eye comparison is provided in Table 2. There were no significant differences in any of the baseline clinical characteristics, including age, self-reported history of diabetes mellitus and systemic hypertension, IOP, presence of DH, and VF parameters (all $P > 0.05$). The inter-observer ICC values were 0.995 (95% CI; 0.993 - 0.997) for the presence of DH and 0.994 (95% CI; 0.990 - 0.997) for the presence of PPA.

Table 1. Comparison of Demographic and Clinical Characteristics of Primary Open-angle Glaucoma Study Eyes

	Unilateral VFD (n=21)	Bilateral VFD within same VF hemifield (n=20)	Bilateral VFD within opposite hemifield (n=20)	*P* value
Demographic data				
Age, (yrs)	55.1 ± 12.6 (32–82)	59.4 ± 12.8 (35–88)	55.0 ± 10.9 (39-80)	0.43
Male, *n* (%)	13 (61.9)	8 (40.0)	7 (35.0)	0.19
Hypertension, n (%)	5 (23.8)	5 (25.0)	1 (5.0)	0.19
Diabetes mellitus, n (%)	5 (23.8)	4 (20.0)	4 (20.0)	0.38
Follow-up duration (yrs)	7.2 ± 2.8 (5–12)	7.7 ± 2.6 (5–13)	7.5 ± 2.5 (5–12)	0.80
Mean glaucoma medications	2.3 ± 1.2 (1–4)	2.1 ± 1.0 (1–4)	2.3 ± 1.8 (1–4)	0.71
Clinical data				
Spherical equivalence (diopters)	–3.10 ± 2.98 (–6.00 to 2.63)	–2.73 ± 3.06 (–6.00 to 1.37)	–2.79 ± 3.73 (–6.00 to 0.50)	0.59
Axial length (mm)	24.93 ± 1.85 (22.31–25.91)	25.51 ± 1.43 (22.40–26.02)	25.27 ± 1.79 (22.96–26.21)	0.55
Central corneal thickness (μm)	535.6 ± 35.5 (443-628)	526.0 ± 30.4 (482–590)	507.2 ± 45.5 (423–580)	0.12
Baseline IOP (mmHg)	17.6 ± 6.3 (9–25)	17.6 ± 4.5 (10–23)	15.9 ± 4.0 (9–23)	0.42
Mean follow-up IOP (mmHg)	14.7 ± 2.4 (10.1–19.3)	14.5 ± 2.5 (10.1–19.3)	13.0 ± 1.7 (10.1–19.3)	0.07
IOP fluctuation (mmHg)	2.3 ± 1.3 (1.0–4.3)	2.2 ± 0.8 (1.1–4.2)	1.9 ± 0.5 (1.0–3.1)	0.48
Cup-to-disc ratio	0.73 ± 0.03 (0.49–0.90)	0.78 ± 0.02 (0.58-0.91)	0.77 ± 0.02 (0.61–0.93)	0.74
Optic disc hemorrhage, n (%)	12 (57.1)	6 (30.0)	6 (30.0)	0.10
Parapapillary atrophy, n (%)	20 (95.2)	19 (95.0)	19 (95.0)	0.36
MD (dB)	–8.15 ± 1.54 (–11.7 to –6.0)	–8.75 ± 1.80 (–11.8 to –6.1)	–8.92 ± 2.08 (–11.9 to –6.1)	0.41
PSD (dB)	12.37 ± 2.84 (8.6–17.1)	11.94 ± 2.76 (6.3-17.2)	10.77 ± 2.58 (6.9-15.2)	0.16
VFI (dB)	75.3 ± 8.1 (61–89)	74.1 ± 10.6 (57–90)	79.6 ± 7.2 (62–91)	0.15

Comparison was performed using one-way ANOVA with post hoc Bonferroni correction for multiple comparisons. Values with statistical significance are shown in bold.

VFD, visual field defect; IOP, intraocular pressure; MD, mean deviation; dB, decibel; PSD, pattern standard deviation; VFI, visual field index

Table 2. Comparison of clinical characteristics between study eyes and contralateral eyes in primary open-angle glaucoma patients

	Unilateral VFD (n=21)			Bilateral VFD within opposite VF hemifield (n=20)			Bilateral VFD within same VF hemifield (n=20)		
	Study	Contralateral	*P* value	Study	Contralateral	*P* value	Study	Contralateral	*P* value
Spherical equivalence (D)	-3.10 ± 2.98	-3.04 ± 2.91	0.86[a]	-2.79 ± 3.73	-2.72 ± 3.77	0.84[a]	-2.73 ± 3.06	-2.66 ± 2.29	0.81[a]
Axial length (mm)	24.93 ± 1.85	24.87 ± 1.76	0.82[a]	25.27 ± 1.79	25.26 ± 1.79	0.98[a]	25.51 ± 1.43	24.31 ± 1.17	0.91[a]
CCT (μm)	535.6 ± 35.5	540.7 ± 28.5	0.84[a]	507.2 ± 45.5	507.9 ± 45.9	0.97[a]	526.0 ± 30.4	525.3 ± 28.9	0.84[a]
Baseline IOP (mmHg)	17.6 ± 6.3	16.1 ± 3.1	0.59[a]	15.9 ± 4.0	16.1 ± 3.1	0.88[a]	17.6 ± 4.5	17.4 ± 4.4	0.90[a]
Mean IOP (mmHg)	14.7 ± 2.4	14.5 ± 1.8	0.78[a]	13.0 ± 1.7	14.5 ± 1.8	0.80[a]	14.5 ± 2.5	14.6 ± 2.7	0.86[a]
IOP fluctuation (mmHg)	2.27 ± 1.29	2.02 ± 0.86	0.62[a]	1.86 ± 0.53	1.79 ± 0.46	0.80[a]	2.19 ± 0.86	2.28 ± 0.90	0.76[a]
Disc area (mm^2)	1.93 ± 0.13	1.97 ± 0.13	0.52[a]	1.82 ± 0.11	1.89 ± 0.13	0.99[a]	1.90 ± 0.11	1.89 ± 0.13	0.38[a]
Cup-to-disc ratio	0.73 ± 0.03	0.70 ± 0.04	0.39[a]	0.77 ± 0.02	0.76 ± 0.02	0.25[a]	0.78 ± 0.02	0.74 ± 0.03	0.09[a]
Disc hemorrhage, n (%)	12 (57.1)	6 (28.6)	0.06[b]	6 (30.0)	6 (30.0)	0.60[b]	6 (30.0)	4 (20.0)	0.60[b]
PPA, n (%)	20 (95.2)	20 (95.2)	0.32[b]	19 (95.0)	19 (95.0)	0.99[b]	19 (95.0)	19 (95.0)	0.80[b]
PPA-to-disc ratio	0.75 ± 0.08	0.36 ± 0.06	**<0.001**[a]	0.48 ± 0.08	0.46 ± 0.05	0.86[a]	0.26 ± 0.03	0.29 ± 0.04	0.54[a]
MD (dB)	–8.15 ± 1.54	–0.66 ± 1.58	**<0.001**[a]	–8.92 ± 2.08	–8.55 ± 2.16	0.51[a]	–8.75 ± 1.80	–7.79 ± 1.60	0.06[a]
PSD (dB)	12.37 ± 2.84	1.86 ± 0.37	**<0.001**[a]	10.77 ± 2.58	9.04 ± 3.60	0.40[a]	11.94 ± 2.76	11.22 ± 3.08	0.24[a]
VFI (dB)	75.3 ± 8.1	98.7 ± 1.4	**<0.001**[a]	79.6 ± 7.2	82.9 ± 9.6	0.48[a]	74.1 ± 10.6	75.3 ± 12.5	0.72[a]

Comparison was performed using [a] t-Test and [b] Chi-square Test. Bonferroni correction for multiple comparisons. Values with statistical significance are shown in bold.

D, diopters; CCT, central corneal thickness; IOP, intraocular pressure; PPA, parapapillary atrophy; MD, mean deviation; dB, decibel; PSD, pattern standard deviation; VFI, visual field index

3.2. Comparison of Inter-Eye Asymmetry Indices

Table 3 summarizes the comparison of inter-eye visual-sensitivity asymmetry index among the three groups at baseline. The iMAI was significantly greater in the unilateral VFD group relative to the groups of bilateral VFD within same and opposite VF hemifield group (7.49 ± 1.20 vs. 3.07 ± 1.45 vs. 2.75 ± 1.53 dB, P<.001), as was the iMAR (13.07 ± 3.01 vs. 0.37 ± 0.04 vs. 0.33 ± 0.05, P<0.001). Additionally, ihVAI was significantly greater in the unilateral VF group, followed by the bilateral VFD within same and opposite VF hemifield group (12.51 ± 4.06 vs. 9.28 ± 4.31 vs. 5.87 ± 3.52, P<0.001), as was the ihVAR (15.58 ± 6.01 vs. 8.42 ± 1.82 vs. 0.53 ± 0.38, P<0.001).

Table 3. Comparison of Inter-eye Visual-Sensitivity Asymmetry Index

	Unilateral VFD (A) (n=21)	Bilateral VFD within same VF hemifield (B) (n=20)	Bilateral VFD within opposite VF hemifield (C) (n=20)	*P* value	Post hoc Analysis
iMAI (dB)	7.49 ± 1.20	3.07 ± 1.45	2.75 ± 1.53	**<0.001**	B, C<A
iMAR	13.07 ± 3.01	0.37 ± 0.04	0.33 ± 0.05	**<0.001**	B, C<A
ihVAI (dB)	12.51 ± 4.06	5.87 ± 3.52	9.28 ± 4.31	**<0.001**	B<C<A
ihVAR	15.58 ± 6.01	0.53 ± 0.38	8.42 ± 1.82	**<0.001**	B<C<A

Comparison was performed using one-way ANOVA with post hoc Bonferroni correction for multiple comparisons. Values with statistical significance are shown in bold.

VFD, visual field defect; iMAI, Inter-eye Mean deviation Asymmetric Index; iMAR, Inter-eye Mean deviation Asymmetric Ratio; ihVA , Inter-eye Hemifield Visual-sensitivity Asymmetric Index; ihVAR, Inter-eye Hemifield Visual-sensitivity Asymmetric Ratio; dB, decibel

3.3. Comparison of Visual Field Progression

During the 7.6 ± 2.4-year follow-up period, 14 of 21 unilateral VFD eyes (66.7%), 7 of 20 bilateral VFD eyes within the opposite VF hemifield (35.0%), and 4 of 20 bilateral VFD eyes within the same VF hemifield (20.0%) showed progression (P=0.007). Kaplan-Meier survival analysis revealed that patients with unilateral VFD had a greater cumulative probability of progression than those with bilateral VFD within same and opposite VF hemifield group (P=0.012) (Figure 1). The overall mean rates of MD change were significantly faster in the unilateral VFD group compared to the bilateral VFD within same and opposite VF hemifield group: −1.06 ± 0.92 vs. -0.45 ± 0.69 vs. −0.37 ± 0.43 dB/year, P=0.001 (Table 4).

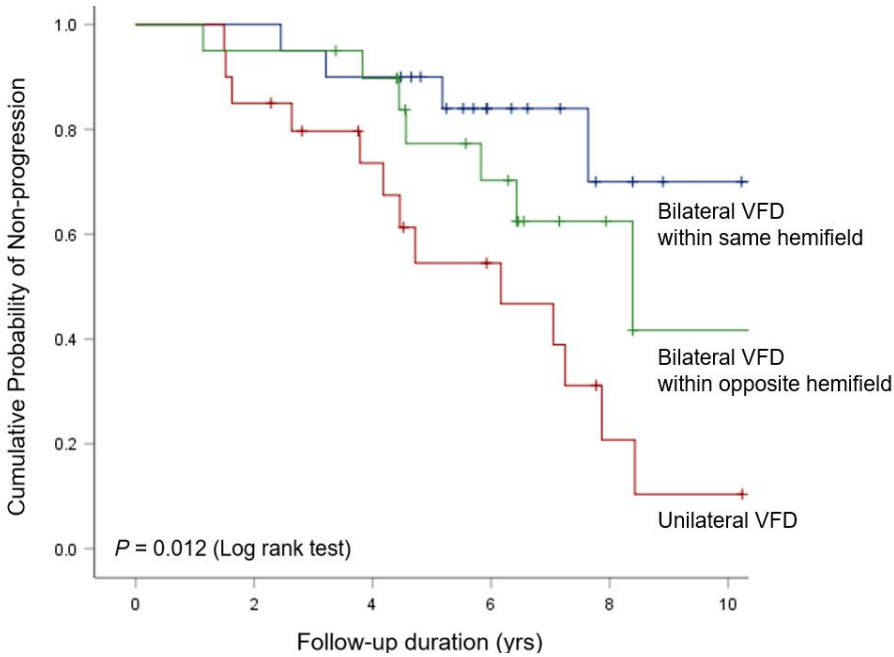

Figure 1. Kaplan-Meier curves comparing cumulative progression probability. Patients with unilateral visual field defect (VFD) had a greater cumulative progression probability than those with bilateral VFD within same and opposite hemifield defect. (P = 0.012, log-rank test).

Table 4. Comparison of Visual Field Progression

	Unilateral VFD (A) (n=21)	Bilateral VFD within same VF hemifield (B) (n=20)	Bilateral VFD within opposite VF hemifield (C) (n=20)	*P* value	Post hoc Analysis
GPA progression, n (%)	14 (66.7)	4 (20.0)	7 (35.0)	**0.009**	B, C< A
MD rate, dB/year	–1.06 ± 0.92	–0.37 ± 0.43	–0.45 ± 0.69	**0.001**	A<B, C

Comparison was performed using one-way ANOVA with post hoc Bonferroni correction for multiple comparisons. Values with statistical significance are shown in bold.
VFD, visual field defect; GPA, Guided Progression Analysis; MD, mean deviation; dB, decibel

3.4. Factors Associated with Glaucoma Progression

The iMAI presented a significant association with MD rate of change (Figure 2, R2=0.082, P=0.025). Comparing the asymmetry indices, the AUC for diagnostic probability of glaucoma progression was determined: iMAI had the best predictive power (0.735), followed by ihVAI (0.734) (Figure 3). By univariate and multivariate Cox proportional hazard models, the presence of DH (HR=2.346, P=0.049), greater iMAI (HR = 1.230, P = 0.011), and greater ihVAI (HR = 1.131, P = 0.007) were significant factors of glaucoma progression (Table 5).

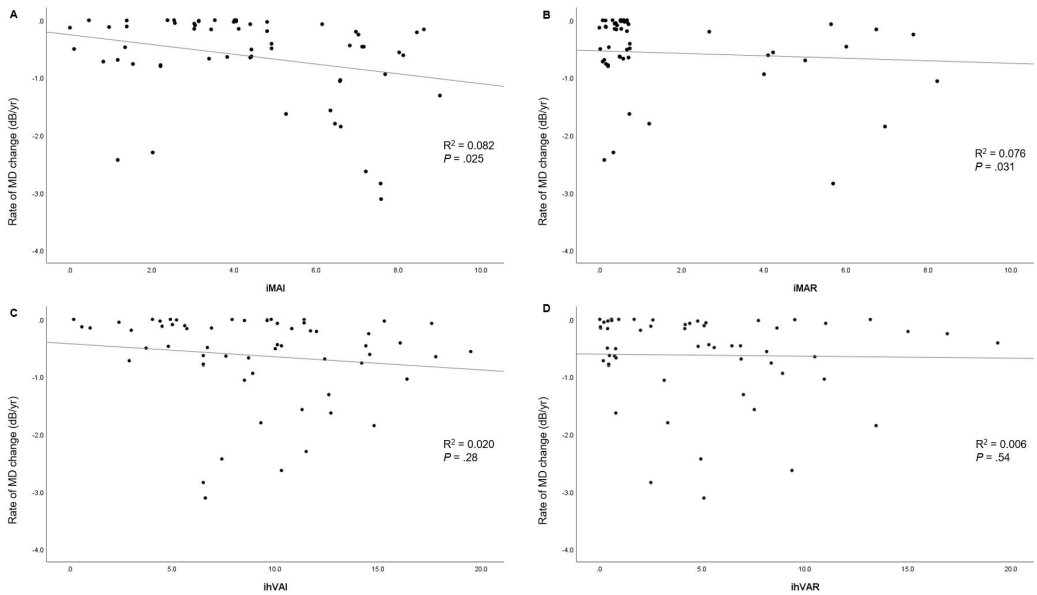

Figure 2. Scatterplots demonstrating relationships between new indices (A: Inter-eye MD Asymmetry Index, iMAI; B: Inter-eye MD Asymmetry Ratio, iMAR; C: Inter-eye hemifield Visual-sensitivity Asymmetry Index, ihVAI; D: Inter-eye hemifield Visual-sensitivity Asymmetry Ratio, ihVAR) and rate of visual field mean deviation (MD) loss by linear regression analysis. The black line is the best-fit linear regression line.

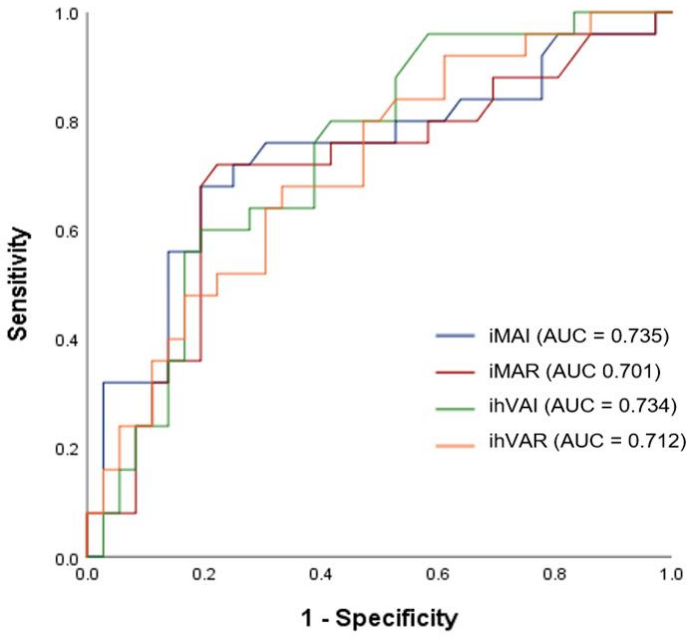

Figure 3. Receiver operating characteristic curves for new indices predicting glaucoma progression.

Table 5. Cox Proportional Hazard Model for Glaucoma Progression

Variable	Univariate model		Multivariate model with iMAI included		Multivariate model with ihVAI included	
	HR (95% CI)	*P* value	HR (95% CI)	*P value*	HR (95% CI)	*P value*
Demographic variables						
Age, yrs	0.984 (0.951-1.019)	0.37				
Sex, male	0.736 (0.329-1.650)	0.46				
Hypertension	0.936 (0.348-2.515)	0.94				
Diabetes mellitus	0.560 (0.075-4.176)	0.56				
Follow-up duration, yrs	0.810 (0.661-0.994)	0.10				
Clinical variables						
Spherical equivalence, diopters	0.973 (0.845-1.117)	0.97				
Axial length, mm	1.076 (0.803-1.442)	0.62				
CCT, μm	0.999 (0.990-1.008)	0.83				
Baseline IOP, mmHg	0.994 (0.929-1.063)	0.86				
Mean IOP, mmHg	0.998 (0.851-1.172)	0.98				
IOP fluctuation, mmHg	0.985 (0.690-1.408)	0.94				
Optic disc hemorrhage	**2.425 (1.030-5.708)**	**0.042**	2.149 (0.913-5.059)	0.08	**2.346 (1.001-5.550)**	**0.049**
Parapapillary atrophy	0.299 (0.039-2.278)	0.30				
Functional parameters						
Baseline MD, dB	0.958 (0.805-1.141)	0.63				
Baseline PSD, dB	1.137 (0.962-1.343)	0.13				
Baseline VFI, %	0.996 (0.955-1.038)	0.84				
Inter-eye VF index						
iMAI, dB	**1.246 (1.064-1.458)**	**0.006**	**1.230 (1.049-1.443)**	**0.011**		
ihVAI, dB	**1.130 (1.035-1.234)**	**0.006**			**1.131 (1.033-1.237)**	**0.007**

Factors with P < 0.10 in the univariate analysis were included in the multivariate analysis. Values with statistical significance are shown in bold.
HR, hazard ratio; CI, confidence interval; CCT, central corneal thickness; IOP, intraocular pressure; MD, mean deviation; dB, decibels; PSD, pattern standard deviation; VFI, visual field index; VF, visual field; iMAI, Inter-eye Mean deviation Asymmetric Index; ihVAI, Inter-eye Hemifield Visual-sensitivity Asymmetric Index

3.5. Representative Cases

Representative cases of POAG in each group are presented in Figure 4 (unilateral VFD, bilateral VFD within same hemifield, and opposite hemifield) during a follow-up period of 5 years.

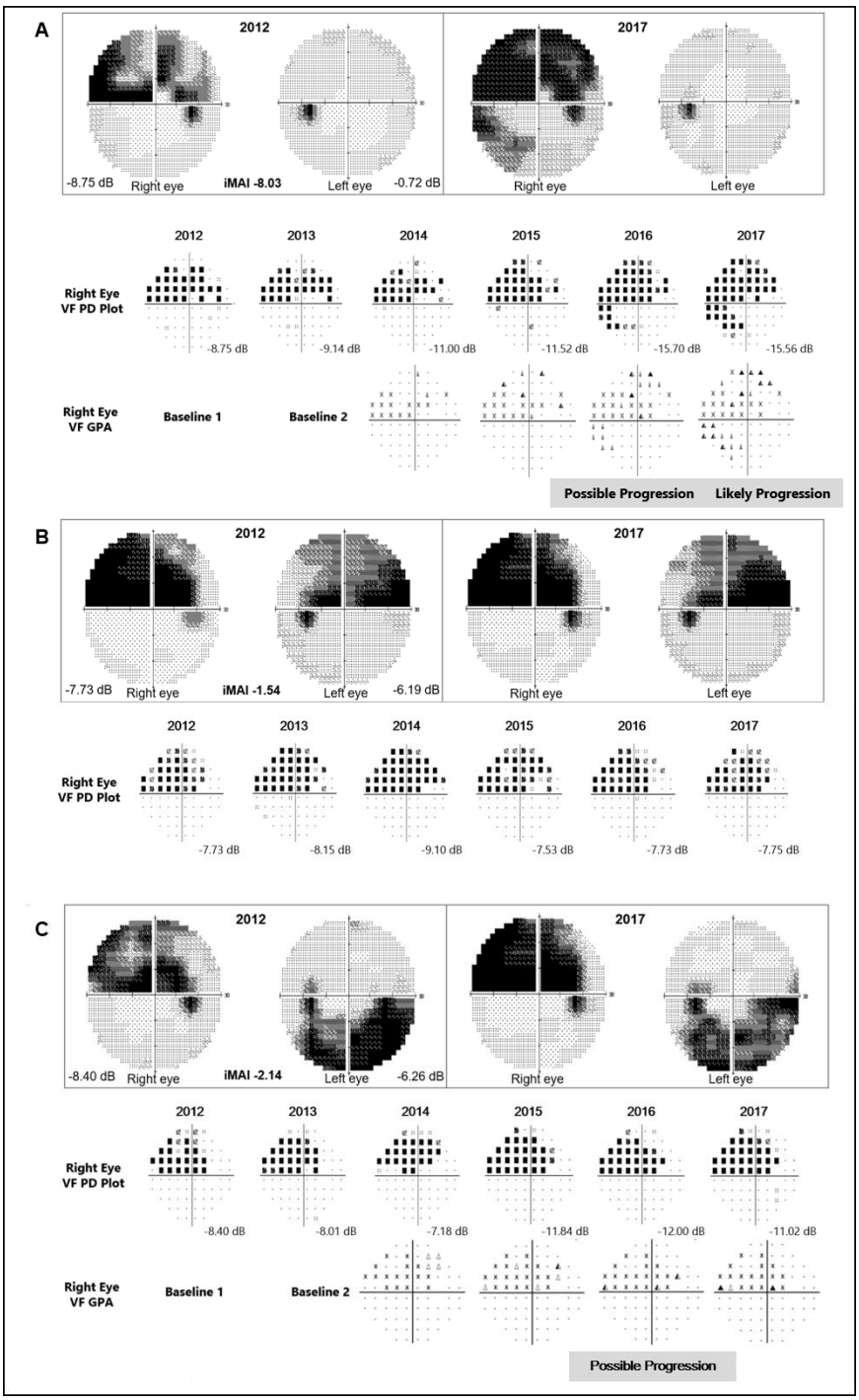

Figure 4. Representative cases of primary open-angle glaucoma with (A) unilateral visual field defect (VFD), (B) bilateral VFD within same hemifield, (C) bilateral VFD within opposite hemifield.

Chapter 4. Discussion

In the current longitudinal study, we compared the rate of disease progression in POAG patients with inter-eye asymmetric and symmetric VFD. Eyes with unilateral VFD showed greater probability and faster rates of VF progression than did eyes with bilateral VFD over the course of a mean 7.6 years of follow-up. More interestingly, a positive association between the degree of VFD asymmetry index and the probability of glaucomatous progression in POAG eyes was established. To our knowledge, this is the first study to suggest the VFD asymmetry index between eyes as a risk factor for glaucoma progression.

Previous studies have defined asymmetric VFD based on an inter-eye MD difference of at least 2 to 6 dB, and symmetric VFD as being less than that MD difference.[13, 17, 28, 29] Meanwhile, our study presented asymmetry by first categorizing the pattern of VFD and afterwards calculating the novel asymmetry index based on the inter-eye MD difference (total and hemifield). The inter-eye VFD patterns were introduced to categorize the possible hemifields affected by GHT, and new indicies were devised to present the inter-eye MD difference with quantitative values. The unilateral VFD pattern presented a minimum iMAI of 6 dB, with significantly greater iMAI and ihVAI compared with the bilateral asymmetric and bilateral symmetric VFD patterns (iMAI: -7.49 vs. -2.75 vs. -3.07 dB; ihVAI: -12.51 vs. -9.28 vs. -5.87 dB; all $P<0.001$). A greater probability of glaucoma progression with faster rates of VF progression was demonstrated in unilateral VFD pattern eyes. Therefore, these finding suggest that a high inter-eye asymmetry index may be associated, at least in part, with higher probability and faster rates of disease progression.

This study found that novel inter-eye asymmetry indices were strongly

associated with glaucoma progression. The reason is not yet clear. However, the positive association between high asymmetry index and glaucoma progression can be explained by use of the better eye with suppression of the worse eye, which may accelerate the progression of visual sensitivity deficit in the worse eye. Amblyopia, defined as degradation of spatial vision in the absence of any detectable organic cause, results from disuse of inadequate foveal or peripheral retinal stimulation and/or abnormal binocular interaction.[30, 31] Stronger suppression of the amblyopic eye has been associated with poorer amblyopic eye visual function. To overcome the issue in adults, neuroplasticity and perceptual learning has been shown to enhance visual function by increasing the efficiency of neural processing, which has also been studied in a variety of ophthalmic disorders such as optic neuropathy.[32-34] Although amblyopia and glaucoma are not the same disease entity, the fundamental idea lying behind the concept of those disease entities potentially gives a new aspect in eyes with inter-eye asymmetric glaucoma. In fact, suppression of visual sensitivity deficit may address a wide variety of mechanisms in glaucoma, and further studies are warranted.

Inter-eye asymmetry such as in IOP, myopia, ONH parameters, RNFL thickness, inter-eye vessel density, vessel narrowing, and VF, has been an issue in glaucoma.[14, 16-20] Cartwright and Anderson reported that in asymmetric normal-tension glaucoma (NTG), eyes with higher IOP showed greater glaucomatous damage than eyes with lower IOP.[35] In the Low-Pressure Glaucoma Study, however, there was no correlation between baseline IOP asymmetry and VF damage in NTG.[36] It is assumed that glaucoma is a multifactorial disorder having multiple active mechanisms. Through the present study, we addressed the issue of another mechanism, this one related to inter-eye VFD asymmetry, which may contribute to disease progression.

The present study has possible limitations to be considered. First, our findings were based on a limited sample size in a single center, and all of the subjects were Koreans. Second, selecting patients with moderate glaucoma and single-hemifield defect may have entailed potential selection bias. Additionally, a high proportion of patients was diagnosed with NTG (80.6%), which might have influenced the results. Third, one may wonder about the possibility of amblyopia at the baseline. However, we included patients with BCVA over 20/30 in both eyes, and the inter-eye BCVA difference was less than two lines. Fourth, the present study did not consider other systemic vascular disorders such as migraine and small ischemic lesions in the brain. Systemic vascular abnormalities affecting both eyes may contribute to glaucoma progression.

In conclusion, inter-eye VFD asymmetry played a role in glaucoma progression. A greater inter-eye asymmetry index showed a greater probability and faster rate of glaucoma progression. Further studies determining whether augmented or differentiated treatment strategies would be beneficial for glaucoma patients with asymmetric VFD are needed.

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262-267.

2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121:2081-2090.

3. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. Ophthalmology 1998;105:2099-2104.

4. Gordon MO, Torri V, Miglior S, et al. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. Ophthalmology 2007;114:10-19.

5. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology 2004;111:1627-1635.

6. Nicolela MT, Drance SM, Rankin SJ, Buckley AR, Walman BE. Color Doppler imaging in patients with asymmetric glaucoma and unilateral visual field loss. Am J Ophthalmol 1996;121:502-510.

7. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701-713; discussion 829-730.

8. Budenz DL, Anderson DR, Feuer WJ, et al. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. Ophthalmology 2006;113:2137-2143.

9. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I. Results of the European Glaucoma Prevention Study. Ophthalmology 2005;112:366-375.

10. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma

trial. Ophthalmology 2007;114:1965-1972.
11. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. Ophthalmology 1999;106:653-662.
12. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration.The AGIS Investigators. Am J Ophthalmol 2000;130:429-440.
13. De Leon JM, Cheung CY, Wong TY, et al. Retinal vascular caliber between eyes with asymmetric glaucoma. Graefes Arch Clin Exp Ophthalmol 2015;253:583-589.
14. Poinoosawmy D, Fontana L, Wu JX, Bunce CV, Hitchings RA. Frequency of asymmetric visual field defects in normal-tension and high-tension glaucoma. Ophthalmology 1998;105:988-991.
15. Lee AJ, Wang JJ, Rochtchina E, Healey P, Chia EM, Mitchell P. Patterns of glaucomatous visual field defects in an older population: the Blue Mountains Eye Study. Clin Exp Ophthalmol 2003;31:331-335.
16. Ong LS, Mitchell P, Healey PR, Cumming RG. Asymmetry in optic disc parameters: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 1999;40:849-857.
17. Lee EJ, Han JC, Kee C. Intereye comparison of ocular factors in normal tension glaucoma with asymmetric visual field loss in Korean population. PLoS One 2017;12:e0186236.
18. Jacobsen AG, Bendtsen MD, Vorum H, Bogsted M, Hargitai J. Normal Value Ranges for Central Retinal Thickness Asymmetry in Healthy Caucasian Adults Measured by SPECTRALIS SD-OCT Posterior Pole Asymmetry Analysis. Invest Ophthalmol Vis Sci 2015;56:3875-3882.
19. Field MG, Alasil T, Baniasadi N, et al. Facilitating Glaucoma Diagnosis With Intereye Retinal Nerve Fiber Layer Asymmetry Using Spectral-Domain Optical Coherence Tomography. J Glaucoma 2016;25:167-176.
20. Hou H, Moghimi S, Zangwill LM, et al. Inter-eye Asymmetry of

Optical Coherence Tomography Angiography Vessel Density in Bilateral Glaucoma, Glaucoma Suspect, and Healthy Eyes. Am J Ophthalmol 2018;190:69-77.
21. Levine RA, Demirel S, Fan J, Keltner JL, Johnson CA, Kass MA. Asymmetries and visual field summaries as predictors of glaucoma in the ocular hypertension treatment study. Invest Ophthalmol Vis Sci 2006;47:3896-3903.
22. Hodapp E, Parrish RK, Anderson DR. Clinical decisions in glaucoma: Mosby Inc; 1993.
23. Mikelberg FS, Drance SM. The mode of progression of visual field defects in glaucoma. Am J Ophthalmol 1984;98:443-445.
24. Chen CL, Bojikian KD, Wen JC, et al. Peripapillary Retinal Nerve Fiber Layer Vascular Microcirculation in Eyes With Glaucoma and Single-Hemifield Visual Field Loss. JAMA Ophthalmol 2017;135:461-468.
25. Longo A, Avitabile T, Uva MG, et al. Morphology of the optic nerve head in glaucomatous eyes with visual field defects in superior or inferior hemifield. Eur J Ophthalmol 2018;28:175-181.
26. Yarmohammadi A, Zangwill LM, Manalastas PIC, et al. Peripapillary and Macular Vessel Density in Patients with Primary Open-Angle Glaucoma and Unilateral Visual Field Loss. Ophthalmology 2018;125:578-587.
27. Yousefi S, Sakai H, Murata H, et al. Asymmetric Patterns of Visual Field Defect in Primary Open-Angle and Primary Angle-Closure Glaucoma. Invest Ophthalmol Vis Sci 2018;59:1279-1287.
28. Feuer WJ, Anderson DR. Static threshold asymmetry in early glaucomatous visual field loss. Ophthalmology 1989;96:1285-1297.
29. Kac MJ, Solari HP, Velarde GC, Brazuna R, Cardoso GP, Ventura MP. Ocular pulse amplitude in patients with asymmetric primary open-angle glaucoma. Curr Eye Res 2011;36:727-732.
30. Lempert P. Retinal area and optic disc rim area in amblyopic, fellow, and normal hyperopic eyes: a hypothesis for decreased acuity in

amblyopia. Ophthalmology 2008;115:2259-2261.
31. McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. J Vis 2003;3:380-405.
32. Hussain Z, Webb BS, Astle AT, McGraw PV. Perceptual learning reduces crowding in amblyopia and in the normal periphery. J Neurosci 2012;32:474-480.
33. Polat U, Schor C, Tong JL, et al. Training the brain to overcome the effect of aging on the human eye. Sci Rep 2012;2:278.
34. Vaitheeswaran K, Kaur P, Garg S. Perceptual Learning for Rehabilitation in Traumatic Optic Neuropathy. Neuroophthalmology 2014;38:88-90.
35. Cartwright MJ, Anderson DR. Correlation of asymmetric damage with asymmetric intraocular pressure in normal-tension glaucoma (low-tension glaucoma). Arch Ophthalmol 1988;106:898-900.
36. Greenfield DS, Liebmann JM, Ritch R, Krupin T. Visual field and intraocular pressure asymmetry in the low-pressure glaucoma treatment study. Ophthalmology 2007;114:460-465.

국문초록

양안 비대칭 시야 장애와 원발개방각녹내장의 진행 분석 연구

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목적: 본 연구는 원발개방각녹내장 환자에서 양안 시야 장애 비대칭에 따른 시야 손상 진행 속도의 연관성을 알아보고자 하였다.

방법: 5년 이상 경과 관찰한 원발개방각녹내장 환자 중, 중기 이상의 녹내장성 반시야결손을 보이는 61명 (122안)이 포함되었다. 초기 시야 패턴에 따라, 세 군으로 나누어 비교하였다: (1) 단안 반시야결손 (2) 양안 대칭 반시야결손 (상측-상측, 하측-하측) (3) 양안 비대칭 반시야결손 (상측-하측). 양안 mean deviation (MD)값 차이를 Inter-eye mean deviation asymmetry index (iMAI)로 정의하였고, 양안 반시야결손의 시감도차이를 inter-eye hemifield visual-sensitivity asymmetry index (ihVAI)로 정의하였다. 시야 손상 진행은 Guided Progression Analysis 소프트웨어를 이용한 사건 기반형 분석 (event-based analysis)과 시야 손상 진행 속도 (MD slope, dB/year)를 통해 계산되었다.

결과: 평균 7.6 ± 2.4 년의 경과 관찰 동안, 시야 손상 진행이 단안 반시야결손군 66.7%, 양안 대칭 반시야결손군 35.0%, 양안 비대칭 반시야결손군 35.0%에서 관찰되었다 (P=0.007). 단안 반시야결손군에서 5년 후 손상 진행 가능성이 55.5%로 유의하게 컸고, MD slope 또한 유의하게 빨랐다 (P = 0.001). MD slope은 큰 iMAI와 연관성을 보였고 (P=0.025), 시신경유두출혈 (P=0.049), 큰 iMAI (P=0.011), 큰 ihVAI (P=0.007)가 녹내장 진행의 위험인자로 나타났다.

결론: 반시야결손을 보이는 원발개방각녹내장 환자에서, 반대안에 상응하는 반시야결손이 없는 눈의 경우 빠른 녹내장 진행을 보였다. 본 연구는 양안 비대칭 시야 장애가 원발개방각녹내장 진행의 위험인자일 가능성을 시사한다.

주요어: 녹내장, 원발성 개방각; 시야; 반시야결손; 비대칭; 진행; 변화 속도; 위험 인자

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