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Development of visual field defect after first-detected optic disc hemorrhage in preperimetric open-angle glaucoma

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Development of visual field defect after first-detected optic disc hemorrhage in preperimetric open-angle glaucoma

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Abstract

Purpose

To evaluate functional progression in preperimetric glaucoma (PPG) with disc hemorrhage (DH) and to determine the time interval between the first-detected DH and development of glaucomatous visual field (VF) defect.

Methods

A total of 87 patients who had been first diagnosed with PPG were enrolled. The medical records of PPG patients without DH (Group 1) and with DH (Group 2) were reviewed. When glaucomatous VF defect appeared, the time interval from the diagnosis of PPG to the development of VF defect was calculated and compared between the two groups. In group 2, the time intervalsfrom the first-detected DH to VF defect ofthe single- and recurrent-DH werecompared.

Results

Of the enrolled patients, 45 had DH in the preperimetric stage.The median time interval from the diagnosis of PPG to the development of VF defectwas 73.3 months in Group 1, versus 45.4 months in Group 2 (P=0.042).The cumulative probability of development of VF defectafter diagnosis of PPG was significantly greater in Group 2 than in Group 1. The median time interval from first-detected DH to the development of VF defect was 37.8 months. The median time interval from DH to VF defect and cumulative probability of VF defect after DH did not show a statistical difference between single

and recurrent-DH patients.

Conclusions

The median time interval between the diagnosis of PPG and the development of VF defect was significantlyshorter in PPG with DH. The VF defect appeared 37.8 months after the first-detected DH in PPG.

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keywords : disc hemorrahge, preperimetric glaucoma

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CONTENTS

Introduction

Preperimetric glaucoma (PPG) is an early stage of open-angle glaucoma defined by the presence of glaucomatous optic disc and retinal nerve fiber layer (RNFL) damage in the absence of visual field (VF) defects on conventional automated perimetry [1]. Although the rate of progressive change in PPG might be relatively slow, PPG can eventually demonstrate significant structural and/or functional progression [2-4].

Disc hemorrhage (DH) is a well-known risk factor for glaucomatous optic nerve damage and its progression [5-9]. It is reported that DH precedes development and progression of RNFL defects [7, 10] and possibly leads to functional deterioration of the VF [9, 11]. Recent studies on long-term follow-up of cases of PPG reveal that DH is a significant risk factor for progression of PPG as well [2, 3].

However, most of the relevant previous studies evaluated glaucoma progression with DH in perimetric glaucoma [6, 8, 9, 12-14]. Overall, DH has been observed more frequently in early than advanced glaucoma and in patients with normal-tension rather than high-pressure glaucoma [15]. A higher prevalence of normal tension glaucoma is reported among Korean patients. Until now, functional progression after first-detected DH in PPG has not yet been adequately investigated. Moreover, there are few reports about the long-term follow-up of functional progression in PPG with DH. In clinical practice, we questioned when VF defects would develop in PPG,

especially if DH is manifested in disc photography. And, we set the hypothesis that the patients with recurrent-DH would show earlier visual field defect than the patients with single-DH. Therefore, the main purposes of this study were to evaluate functional progression in PPG with and without DH and to determine the time interval between first-detected DH and development of glaucomatous VF defects.

Subjects and Methods

Subjects

In this retrospective cohort study, a total of 87 patients from the Glaucoma Clinic of Seoul National University Hospital, Seoul, Korea who had been first diagnosed with PPG between 1997 and 2012 were included. The medical records of PPG patients without DH (Group 1) and with DH (Group 2) were reviewed. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital, Korea.

The subjects of this study met the following inclusion criteria: best-corrected visual acuity of 20/40 or better; spherical equivalent within ± 6.0 diopters; cylindrical error less than 3.0 diopters; open anterior chamber angle on initial examination; reliable VF testing results (fixation loss < 20%, false positive errors < 15%, false-negative errors < 15%). In cases where

both eyes of a patient were eligible for the study, one eye was chosen at random for inclusion. Patients were excluded based on the following criteria: history of ocular surgery (other than uncomplicated cataract surgery); closed or occludable angle on gonioscopic examination; any systemic or ocular pathology (other than primary open-angle glaucoma) potentially affecting the optic dis c, RNFL, or VF (e.g., retinal vascular occlusive disease, diabetic retinopathy, hypertensive retinopathy, uveitis). Later, patients with a total follow-up period less than 30 months or a follow-up interval loss of more than 6 months were also excluded. The enrolled patients were followed-up at 3-6 month intervals.

All subjects underwent a comprehensive ophthalmic examination, including measurement of best-corrected visual acuity and spherical equivalent by automatic refractometry (KR-890; Topcon Corporation, Tokyo, Japan), intraocular pressure (IOP) measurements with Goldmann tonometry, dilated fundus examination, and corneal pachymetry (Pocket II Pachymeter Echo graph; Quantel Medical, Clermont-Ferrand, France). At the baseline examination, all patients also were evaluated with color stereo optic disc photography, red-free RNFL photography, and standard automated perimetry. The long-term IOP fluctuation was defined as the standard deviation of IOP measurement at all visits [16].

PPG was diagnosed when all following criterias were met: presence of typical localized glaucomatous RNFL defect on red-free RNFL photography; glaucomatous optic nerve head change with neuroretinal rim

narrowing, notching and excavation; normal VF on standard automated perimetry on three consecutive initial baseline examinations; open anterior chamber angle on gonioscopy; IOP controlled with/without glaucoma medication and without surgical intervention, and absence of any secondary cause of glaucomatous optic neuropathy. Localized RNFL defects on red-free RNFL photography were determined when their width at a 1-disc-diameter distance from the edge of the disc was larger than a major retinal vessel, diverging in an arcuate or wedge shape and reaching the edge of the disc.

DH was defined as an isolated hemorrhage observed on the optic disc or in the peripapillary retina extending to the disc rim, as diagnosed by clinical examination or color-disc/red-free RNFL photography. The following alternative causes of such hemorrhage were grounds for exclusion: ischemic optic neuropathy, papillitis, retinal vein occlusion, diabetic retinopathy, or posterior vitreous detachment.

Color-disc and Red-free Retinal Nerve Fiber Layer Photography

Color-disc and red-free RNFL photography were obtained following pupil dilation. Until 2005, a TRC-50IA (Topcon Inc., Tokyo, Japan) or CF-60UV (Canon Inc., Utsunomiya, Japan) fundus camera was used. From 2005 onward, the EOS D60 (Canon, Tochigiken, Japan) or VX-10 (Kowa, Optimed, Tokyo, Japan) has been employed. The color-disc and red-free RNFL photographs were independently evaluated by 2 authors (HJK, KHP)

in a random order and in masked fashion, without knowledge of the subjects' clinical information.

Optical Coherence Tomography

From 2005 to 2008, optical coherence tomography (OCT) measurements were performed using the peripapillary fast RNFL program of Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA); since 2008, Cirrus HD-OCT (Carl Zeiss Meditec) was used.

Visual Field Testing

Glaucomatous VF defect was defined as the consistent presence of a cluster of 3 or more contiguous non-edge points on a pattern deviation plot, with a probability of occurring in less than 5% of the normal population ($p < 5\%$), with one of these points having a probability of occurring in less than 1% of the normal population ($p < 1\%$), or a glaucoma hemifield test result outside the normal limits. The VF defect had to be repeatable on at least 3 consecutive tests. Prior to June 2000, a full-threshold program was used to evaluate the central 30-2 perimetry (Humphrey field analyzer; Carl Zeiss Meditec, Dublin, CA, USA); after that date, the VF was evaluated using the Swedish interactive thresholding algorithm (SITA) standard 30-2 program.

Data Analysis

On first appearance of glaucomatous VF defect in the corresponding

hemifield location of RNFL photographs or DH, the median time interval from the diagnosis of PPG to the development of the VF defect was calculated in both groups and compared with the median test and Kaplan-Meier survival analysis. For group 2, the median time interval from the first-detected DH to VF defect was also evaluated and compared between the single-DH and recurrent-DH patients in line with both the median test and Kaplan-Meier survival analysis. The median value, not the average, was used, because the distributions of each time interval were skewed (skewness: 0.490 ± 0.365 for time interval from PPG diagnosis to development of glaucomatous VF defect in Group 1 and 0.884 ± 0.354 in Group 2; 1.036 ± 0.354 for time interval from first-detected DH to development of glaucomatous VF defect in Group 2), and the end-values were not known [17]. Spearman correlation analysis was used to determine the correlation between the number of detected DHs before VF defect and the time interval from the first-detected DH to the development of glaucomatous VF defect. A P value of less than .05 was accepted as statistically significant.

Results

Subject Characteristics

A total of 87 eyes of 87 subjects with PPG were enrolled. Of the enrolled

patients, 45 had DH in the preperimetric stage. All of the subjects were Korean. The total mean follow-up period was 104.1 ± 36.5 months: 101.6 ± 38.7 months in Group 1 (range, 32.4 – 232.0 months), and 106.4 ± 34.6 months in Group 2 (range, 32.4 – 219.3 months), showing no statistically significant difference between the groups. The number of visits and VF exams per year did not show significant differences between the two groups. In Group 2, DH was detected on average 8.09 ± 21.25 months (range, 0 – 95.2 months) after PPG diagnosis. Thirty-five patients showed DH at the diagnosis of PPG. The mean follow-up period after the first-detected DH was 98.3 ± 35.1 months (range, 32.4 – 168.8 months). The mean age of the subjects at PPG diagnosis was 56.6 ± 10.9 years (range, 27 – 75 years), and the mean age at first DH detection was 57.8 ± 11.4 years (Table 1).

Optic Disc Hemorrhage at Preperimetric stage

Over the course of the mean 98.3 month follow-up period after the first-detected DH, 23 (51.1%) of the 45 eyes showed recurrent DH (more than 2 episodes of hemorrhage). The average number of DH detections at the PPG stage was 1.64 ± 0.71. As for the DH location, 88.9% of the eyes showed inferotemporal DH (Table 1). Among 45 patients with DH, 44 patients showed the same RNFL defect position at DH site. One patient with superior and inferior DH and superior VF defect showed inferior RNFL defect.

Development of Glaucomatous Visual Field Defect in PPG with/without Disc Hemorrhage

All cases in this study developed VF defect corresponding hemifield location of DH during the follow-up period. Over the course of the mean 104.1 month total follow-up period, the median time interval between the diagnosis of PPG and the development of glaucomatous VF defect was 73.3 months in Group 1 (range, 19.1 – 162.7 months; interquartile range, 37.8 – 96.8 months), versus 45.4 months in Group 2 (range, 11.4 – 121.2 months; interquartile range, 32.6 – 62.3 months) ($P = 0.042$) (Fig. 1). The cumulative probability of development of VF defect after diagnosis of PPG was significantly greater in Group 2 than in Group 1 ($P = 0.017$, log rank test) (Fig. 2). Until the VF defect development, the MD slope was -0.16±0.58 dB/year in Group 2 and -0.07±0.32 dB/year in Group 1.

For the mean 98.3 months of follow-up period after the first-detected DH, the median time interval between first-detected DH and development of glaucomatous VF defect was 37.8 months (range, 6.0 – 121.2 months; interquartile range, 23.2 – 54.7 months). At the time of glaucomatous VF-defect appearance, the value of the pattern standard deviation (PSD) in the central 30-2 perimetry was significantly higher in Group 2 (Table 1).

Forty-three out of 45 patients (95.55%) in Group 2 and 35 out of 42 patients (83.33%) in Group 1 started medical treatment after diagnosis of PPG. More patients in Group 2 started medical treatment due to the occurrence of DH at the time of PPG diagnosis. The rest in both groups

started medical treatment after the development of VF defect. In Group 2 patients who received medical treatment at the time of PPG diagnosis, the median time interval between first-detected DH and development of glaucomatous VF defect was still 37.8 months. Also, the median time interval between the diagnosis of PPG and the development of glaucomatous VF defect was 75.9 months in Group 1 (range, 19.07 – 162.73 months; interquartile range, 40.20 – 102.83 months), versus 45.4 months in Group 2 (range, 11.4 – 121.2 months; interquartile range, 31.80 – 62.10 months) (P = 0.003).

The median time interval from DH to VF defect did not show a statistical difference between the single-DH (n=22) and recurrent-DH patients (n=23) (33.4 months vs. 43.4 months) (P = 0.647). Kaplan-Meier survival analysis also revealed that there was no statistical difference between the single- and recurrent-DH patients (P = 0.128, log rank test) (Fig. 3). In Group 2, MD slope was -0.23±0.79 dB/year in single DH group and -0.10±0.24 dB/year in recurrent DH group. There was no statistically significant correlation between the number of DHs and the time interval between the first-detected DH and the development of glaucomatous VF defect (P = 0.067). We addressed the cases of DH in PPG in Online Resource 1, 2 and 3.

Discussion

The main purposes of this longitudinal study were to evaluate functional progression in PPG with and without DH and to determine the time interval between first-detected DH and the development of glaucomatous VF defect. The strength of our study was that the mean follow-up period was more than 8 years in both groups (average total follow-up period: 104.1 months; 101.6 ± 38.7 months in Group 1 and 106.4 ± 34.6 months in Group 2) (Table 1). The median time interval from diagnosis of PPG to the development of glaucomatous VF defect was significantly shorter in PPG with DH than in PPG without DH. VF defect appeared 37.8 months after the first-detected DH in PPG.

PPG is an early stage of open-angle glaucoma, and does not appear as an abnormality on standard automated perimetry. As consistent with earlier findings [18, 19], the DHs in the present study were found more often in the inferotemporal location (88.9% of cases). The inferotemporal region is known as a frequent site of earlier glaucomatous damage, and DH is more common in early or moderately advanced glaucoma than in advanced glaucoma [20]. Given the significance and prognostic implications of DH, its evaluation adds clinical utility to the monitoring PPG progression.

In the present study, Group 2 (PPG with DH) showed a significantly shorter median time interval from diagnosis of PPG to development of glaucomatous VF defect than did Group 1 (PPG without DH) (P = 0.042). These results correspond well with those of an earlier study, which reports that DH is a strong predictor of the development of progressive VF loss in

glaucoma [11]. Indeed, the appearance of DH can indicate glaucomatous damage even if the VF initially is unremarkable [7, 18]. Siegner and Netland [18] documented significantly faster VF-defect progression and optic nerve head changes in glaucomatous and ocular hypertension eyes with DH (respective mean time intervals: 16.8 ± 2.0 months and 23.8 ± 2.9 months). However, the majority (86%) of their patients had perimetric glaucoma, and the proportion with ocular hypertension was small (14%).

Recurrent DH might be associated with more extensive glaucomatous changes, though there is some controversy about its clinical significance. We also set the hypothesis that the patients with recurrent-DH would show earlier functional progression. Ishida et al. report that recurrent DH exhibited more progressive VF changes than did single DH [11]. However, Kim and Park found that the cumulative probability of optic disc deterioration, including RNFL changes after DH, was significantly greater in glaucoma patients with recurrent DH than in those with single DH, whereas they noted no significant differences between those 2 groups with regard to the rate of VF deterioration [19]. Siegner and Netland, likewise, report no differences in the rate of progression of optic disc changes or VF defects between recurrent and single DH [18, 21]. De Beaufort HC et al. emphasize that recurrent DH should not be seen as an indicator of worse VF prognosis relative to singly detected DH [22]. In the present study, correspondingly, there was no statistically significant correlation between the number of DHs and the time interval from DH to VF defect ($P = 0.107$).

Moreover, the median time interval from DH to VF defect did not show any statistical difference between the single-DH and recurrent-DH patients. Thus, our results suggest that DH recurrence does not affect the time interval from DH to VF defect in PPG.

Other results from the present study show that at the time of glaucomatous VF-defect appearance and at the final follow-up, the value of the perimetry PSD were significantly higher in Group 2 (PPG with DH) than in Group 1 (PPG without DH). A higher value of PSD indicates an irregular hill of vision and a field with localized defects [23]. Asaoka et al. also report the usefulness of PSD in identifying PPG [24, 25]. When monitoring functional progression in PPG with DH, careful observation of PSD can be helpful.

The Ocular Hypertension Treatment Study highlighted the difficulty of detecting DHs on clinical examination, noting that more than 80% of its photographically documented DHs had been missed with clinical examinations [26]. However, our follow-up was longer-term (average total follow-up period: 104.1 months) than any of the other relevant studies [2-4, 12, 27], and we also evaluated color-disc and red-free RNFL photography. So, our results can impart relevant clinical implications.

There are several limitations to this study. First, we were unable to gain full information on the use of systemic, including anticoagulant medication in most patients [28]. Second, we could not control the use of glaucoma medication during the follow-up in both groups. In fact, most patients in this study (83.33% in Group 1 and 95.55% in Group 2) started medical

treatment after diagnosis of PPG. Even though more patients in Group 2 started medical treatment earlier due to the presence of DH, the median time interval between the diagnosis of PPG and the development of glaucomatous VF defect was significantly shorter in Group 2 than in Group 1 (P = 0.003). Early Manifest Glaucoma Trial [6] demonstrates that IOP-reducing treatment was unrelated to the presence of frequency of DH. They suggest that glaucoma progression in eyes with DH cannot be totally halted by IOP reduction. Our study also shows that the median time interval between first-detected DH and development of glaucomatous VF defect was still 37.8 months in patients who received medical treatment at the time of PPG diagnosis. Finally, structural progression by means of OCT may be meaningful in PPG [29, 30]. In this retrospective cohort study, a total of 87 patients who had been first diagnosed with PPG between 1997 and 2012 were included. However, in our clinic the OCT was introduced in 2005. We, therefore, did not have baseline OCT data before 2005. Also, as described in the Methods, from 2005 to 2008, OCT measurements were performed using Stratus OCT; since 2008, Cirrus HD-OCT was utilized. So, not all patients in this study had sufficient OCT outcomes for the comparison between the two groups. But, in Online Resources, we show OCT measurement changes in a DH group with recent OCT printout. Further controlled prospective studies with structural and functional progression in PPG with DH might be needed.

In conclusion, the median time interval from diagnosis of PPG to

development of VF defect was significantly shorter in PPG with DH than in PPG without DH. The VF defect appeared at 37.8 months after the first-detected DH in PPG.

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Table 1. Clinical Characteristics of Preperimetric Open-angle Glaucoma Eyes with Disc Hemorrhage

Characteristics	**Group 1 (n=42)**	**Group 2 (n=45)**	
	Preperimetric Glaucoma Eyes without DH	**Preperimetric Glaucoma Eyes with DH**	***P* value**
Age at diagnosis (years)	54.67 ± 12.33	56.58 ± 10.88	0.445*
Gender male/female	19/23	18/27	0.668†
Subtypes [no.]			0.553†
Baseline IOP ≤ 21 mmHg	37	37	
Baseline IOP > 21 mmHg	5	8	
Laterality right/left	24/18	24/21	0.830†
Spherical equivalent (Diopters)	-1.68 ± 3.40	-0.11 ± 1.92	0.097*
Central corneal thickness (μm)	533.90 ± 29.52	522.60 ± 24.18	0.165*
Systemic comorbidity			
DM [no. (%)]	4	7	0.524†
HTN [no. (%)]	12	20	0.182†
Number of visit / year	2.97 ± 0.16	2.93 ± 0.12	0.210*
Number of VF exam / year	2.04 ± 0.14	2.03 ± 0.09	0.690*
Baseline VF MD (dB)	-1.18 ± 1.45	-0.88 ± 1.02	0.280
Baseline VF PSD (dB)	1.96 ± 0.46	2.04 ± 0.44	0.427
Long-term IOP fluctuation (mmHg)	1.58 ± 0.61	1.71 ± 0.54	0.326
Total follow-up (months)	101.6 ± 38.7	106.4 ± 34.6	0.538*
Baseline characteristics			
Best-corrected visual acuity (logMAR)	0.02 ± 0.03	0.01 ± 0.05	0.729*
Mean IOP (mmHg)	15.36 ± 3.28	16.45 ± 3.48	0.157*
During follow-up after DH detection			
Number of DH detections		1.64 ± 0.71	
Single (no. eye)		22	
Recurrent (no. eye)		23	
At time of DH detection			
Location [no. eye (%)]			
Superotemporal		4	
Inferotemporal		40	
Both quadrants		1	
At time of VF-defect appearance			
Best-corrected visual acuity (logMAR)	0.08 ± 0.09	0.05 ± 0.08	0.068*
IOP (mmHg)	12.94 ± 2.15	12.64 ± 2.94	0.595*
VF MD (dB)	-1.45 ± 1.62	-1.78 ± 2.10	0.418*
VF PSD (dB)	2.76 ± 0.90	3.58 ± 1.82	**0.011***

DH = disc hemorrhage, DM = diabetes mellitus, HTN = hypertension, IOP = intraocular pressure, MD = mean deviation, PSD = pattern standard deviation, VF = visual field.

*t-test.

†chi-square test.

Figure Legends

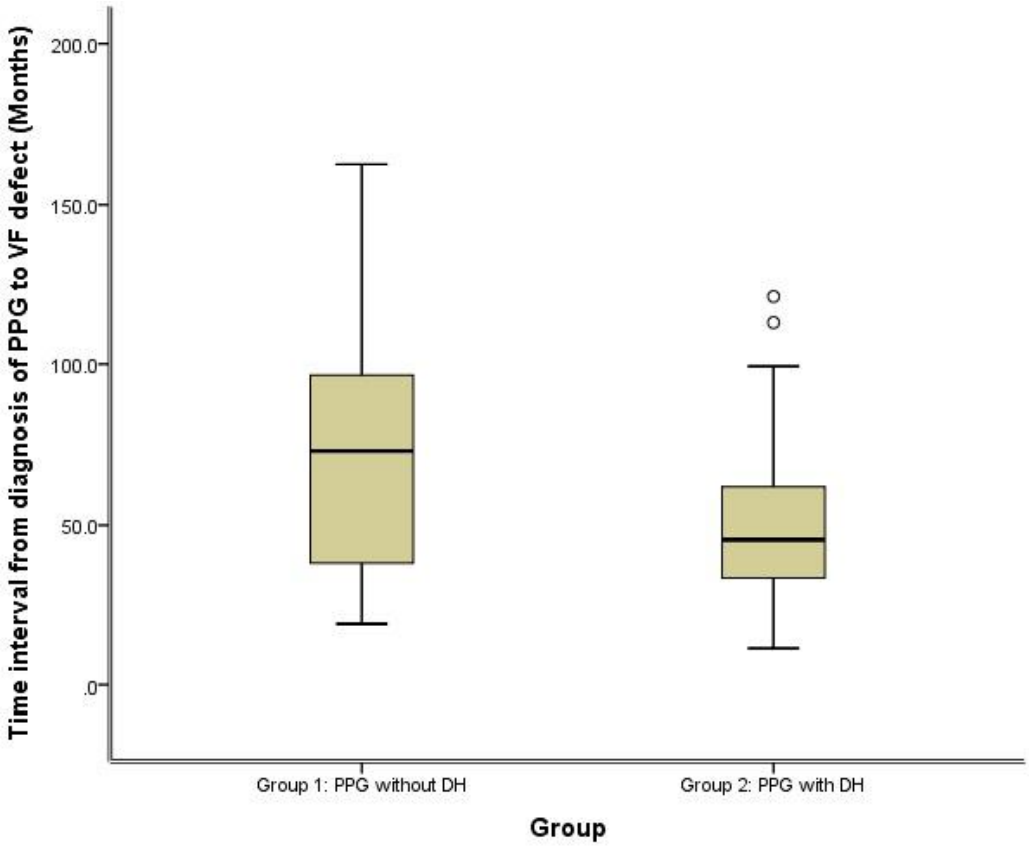

Fig. 1 Boxplot of time interval from diagnosis of preperimetric glaucoma (PPG) to appearance of visual field (VF) defect. The median time interval was 73.3 months in PPG without disc hemorrhage (DH) (range, 19.1 – 162.7 months; interquartile range, 37.8 – 96.8 months) and 45.4 months in PPG with DH (range, 11.4 – 121.2 months; interquartile range, 32.6 – 62.3 months). Two cases (small circles) were excluded from the calculation of the median time interval in Group 2. The P value of the median test was 0.042.

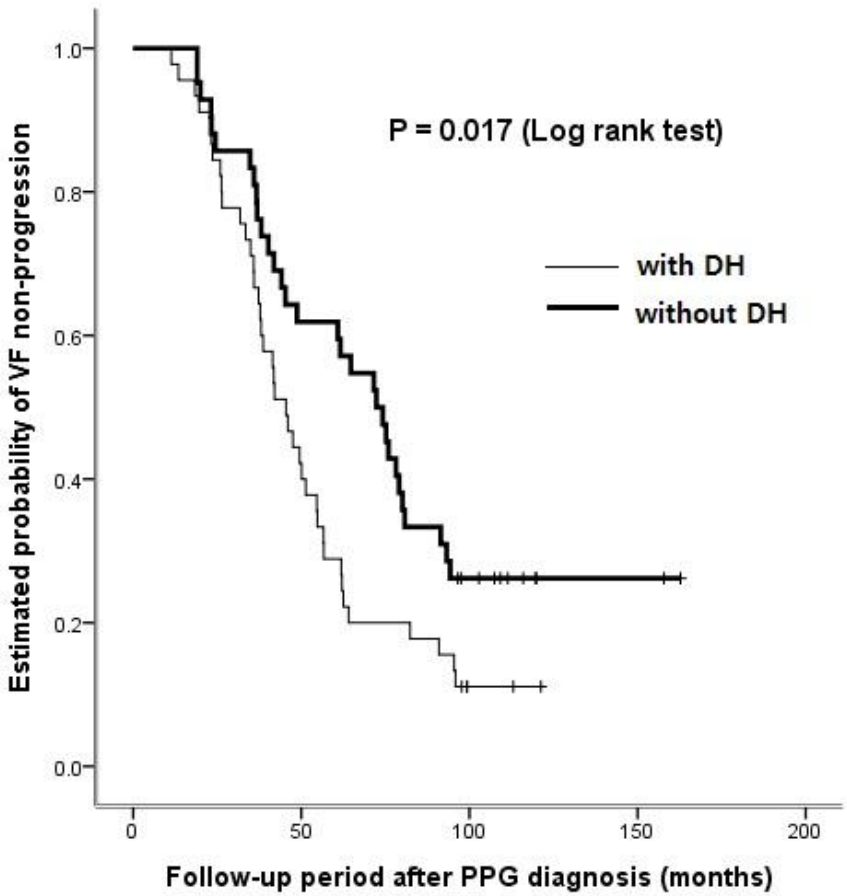

Fig. 2 Kaplan-Meier analysis of the probability to remain without deterioration of visual field (VF) in preperimetric glaucoma (PPG) without and with disc hemorrhage (DH).

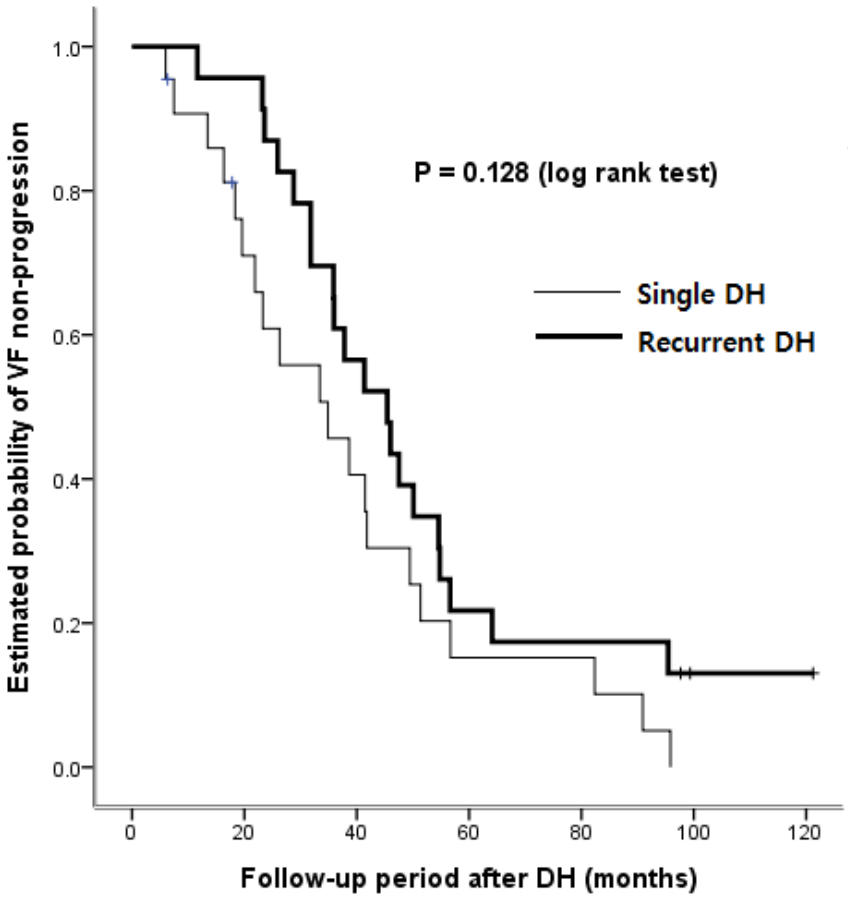

Fig. 3 Kaplan-Meier analysis of the probability to remain without deterioration of visual field (VF) in preperimetric glaucoma patients with single and recurrent disc hemorrhage (DH).

국문초록

목적: 시신경유두출혈이 있는 시야결손 전 녹내장에서 기능적 진행을 평가하고 처음 발견된 시신경유두출혈로부터 시야결손의 발생까지의 시간을 관찰한다.
방법: 시야결손 전 녹내장이 진단된 87명의 환자들 중 시신경유두출혈이 없는 그룹1과 시신경유두출혈이 있는 그룹 2의 의료 기록을 검토하였다. 두 그룹에서 시야결손 전 녹내장의 진단으로부터 녹내장성 시야결손의 발생까지의 시간 간격을 계산하고 이를 비교하였다. 그룹 2에서는, 단일 그리고 반복적인 시신경유두출혈이 있는 환자들 사이에서 처음 발견된 시신경유두출혈로부터 시야결손이 발생하기까지의 시간 간격을 비교하였다.
결과: 87명의 시야결손 전 녹내장 환자들 중 45명에게 시신경유두출혈이 관찰되었다. 시야결손 전 녹내장의 진단으로부터 시야결손의 발생까지 중위 시간 간격은 그룹 1에서 73.3 개월이었고, 그룹 2에서는 45.4 개월이었다 (P=0.042). 시야결손 전 녹내장의 진단 후 시야결손의 발생까지의 누적확률은 그룹 2에서 그룹 1보다 통계적으로 유의하게 높았다. 처음 발견된 시신경유두출혈 후 시야결손의 발생까지의 중위 시간 간격은 37.8 개월이었다. 단일 그리고 반복적인 시신경유두출혈 사이에서는 시신경유두출혈 후 시야결손의 발생까지의 중위 시간 간격, 누적확률 모두 통계적으로 의미있는 차이를 보이지 않았다.
결론: 시야결손 전 녹내장의 진단 후 시야결손의 발생까지 중위 시간 간격은 시신경유두출혈이 있는 군에서 시신경유두출혈이 없는 군보다 의미있게 짧았다. 시야결손 전 녹내장에서 처음 발견된 시신경유두출혈 후 시야결손의 발생은 37.8 개월 후 나타났다.

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주요어 : 시신경유두출혈, 시야결손 전 녹내장
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