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ARTICLE

Progression patterns of normal-tension glaucoma groups classified by hierarchical cluster analysis

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Abstract

Objectives To investigate differences in progression patterns of normal-tension glaucoma (NTG) patients in three clusters classified by hierarchical cluster analysis (HCA).

Materials and methods In a retrospective study, 200 eyes of NTG patients classified by HCA in 2015 who were followed up to the current date were evaluated. Peripapillary retinal nerve fibre layer (RNFL) thicknesses were measured by Cirrus HD-OCT and progression rate was calculated by trend analysis (Guided Progression Analysis [GPA]). VF progression rate was evaluated by linear regression analysis of mean deviation (MD). Progression patterns of three clusters were compared by histograms.

Results In total, 153 eyes of 153 patients were followed up. Mean observation period was 5 years. RNFL reduction rate was −0.83 µm/year in cluster 1, which showed early glaucomatous damage in previous reports; −0.45 µm/year in cluster 2, which showed moderate glaucomatous damage; and −0.36 µm/year in cluster 3, which showed young and myopic glaucomatous damage. The progression pattern of cluster 3 showed a double-peak distribution; RNFL reduction rate was 0.11 µm/year in the non-progressive group and −1.07 µm/year in the progressive group.

Conclusion The progression patterns were different among three NTG groups that were divided by HCA. In particular, the group of young and myopic eyes showed a mixture of two different patterns.

Introduction

Normal tension glaucoma (NTG) is a disease with different progression rates for each patient and is underpinned by various causes. According to the Collaborative Normal Tension Glaucoma study (CNTGS), NTG in half of the untreated patients did not progress for 5–7 years [1]. NTG is a disease underscored by several pathologies [2]. As such, the characteristics of NTG should be classified with greater detail. We conducted a preliminary study 5 years ago using hierarchical cluster analysis (HCA) to subdivide NTG [3].

HCA is an analytical method in which similar characteristics are identified and divided into clusters by an automated computer programme [4, 5]. In our preceding investigation, we analysed six optic nerve head (ONH) parameters and retinal nerve fibre layer (RNFL) thicknesses obtained from spectral-domain optical coherence tomography (SD-OCT), culminating in three clusters (Supplementary Fig. 1). We studied 200 eyes of 200 NTG patients, and the features of each cluster are as follows: the ONH parameters that formed classification criteria exhibited clear differences between clusters 1 and 2. Cluster 1 has small cupping with thick RNFL, and cluster 2 has the opposite features. According to this tendency, the mean deviation (MD) of cluster 1 (−3.12 ± 4.10 dB) exhibited early glaucoma findings, and that of cluster 2 (−6.42 ± 5.50 dB) exhibited moderate glaucoma findings. Cluster 3 was located mid-position between the other measures and was younger with myopic changes when

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compared with clusters 1 and 2. We focused on cluster 3 at that time and predicted that glaucoma progression patterns would be different from those of other clusters [3]. However, there were no studies that analysed the difference in progression pattern of NTG using OCT, we could not predict if their progress would be really different, especially in cluster 3. The purpose of this study was to explore whether the progression pattern of the three clusters classified by ONH parameters in preceding research differed. Thus, we followed changes in patients over the course of the past 5 years.

Materials and methods

Study design

This retrospective, single-centre study was performed on patients classified by HCA 5 years ago. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Severance Hospital.

Initially, we enroled 200 eyes of 200 NTG patients who were followed up for more than 3 years from March 2011 through June 2012. After a retrospective review of medical records, we identified a final total of 153 patients from the initial 200 patients and performed follow-up until the study timepoint.

Inclusion criteria were as follows: (1) treatment and a follow-up period of at least 3 years after the diagnosis of NTG with visits at 3– 6-month intervals; (2) at least five reliable visual field (VF) tests were available excluding the first two tests affected by learning effects, with reliable VF tests (fixation losses <20%, false positive rate <15%, and false negative rate <20%); (3) at least five optical coherence tomography (OCT) tests were available, and OCT scans had images that were clear enough to detect scan circle and signal strength of at least 6; (4) at least five intraocular pressure (IOP) measures by goldmann applanation tonometer were available; (5) IOP was kept below 21 via topical medication during the follow-up period.

Exclusion criteria were as follows: (1) patients with media opacities precluding good quality OCT; (2) other diseases potentially affecting the VF (macular disorders, neurological disease, etc.); (3) any history of intra-ocular surgery other than uncomplicated cataract surgery; (4) a history or evidence of other optic neuropathies.

All patients underwent the following tests upon their initial visit: slit-lamp biomicroscopy, gonioscopy, applanation tonometer for IOP, autorefraction keratometry (RK-3; Canon, Lake Success, NY) to check refractive error (spherical equivalent), ultrasonic phacymetry (DGH-1000; DGH Technology, Frazer, PA) to measure central corneal thickness (CCT), IOL master (Carl Zeiss Meditec, Jena, Germany) to measure axial length (AL), colour disc stereophotography, red-free fundus photography (CF-60UVi; Canon Inc., Utsunomiya, Japan), and dilated fundus examination with a 90D lens to eliminate any other retinal disease. A single experienced technician performed automated perimetry using the Humphrey Visual Field Analyzer (30-2 SITA Standard algorithm; Carl Zeiss Meditec). The SD-OCT (Cirrus HD-OCT, software version 6.0.0; Carl Zeiss Meditec) was used to evaluate RNFL thickness and optic disc appearance. After the first visit, colour disc stereophotography, red free fundus photography, VF test and OCT were evaluated at intervals of 3–12 months, according to the patient's status.

SD-OCT imaging and progression rate measurements

A single trained operator performed SD-OCT in our clinic for all individuals. After pupil dilation, ONH parameters and RNFL thickness were determined using the optic disc cube protocol (software version 6.0.0), which generated a cube of data over a 6×6 mm grid by acquiring a series of 200 A-scans from 200 linear B-scans (40,000 points).

The RNFL algorithm produced standardised RNFL thickness within the same 3-dimensional data cube. A calculation circle, which was 3.46 mm in diameter and consisted of 256 A-scans, was automatically positioned around the optic disc for analysis, and averaging of these A-scan measurements was performed to obtain RNFL thicknesses. The SD-OCT scans were re-examined if the signal strength was <6, if the image lacked sharp uniform focus, or if artefacts were present.

The Cirrus HD-OCT GPA (Carl Zeiss Meditec, software version 9.5) provides event and trend analysis to detect progressive decreases in peripapillary RNFL, termed guided progression analysis [6]. We measured the progression rate on OCT using a trend analysis that evaluated the rate of change in RNFL thickness (average, superior and inferior) over time with linear regression analysis. We excluded data in cases of algorithm segmentation failure, signal strength less than six or lack of focus on the fovea.

Visual field progression rate measurements

The progression rate of VF defects was evaluated according to the MD slope of the Humphrey Field Analyzer. Linear regression of sensitivity (in dB) was performed according to all fields until the final examination. We excluded the first two field tests prior to enrolment to minimise learning effects.

Table 1 Baseline optic nerve head parameters and retinal nerve fibre layer (RNFL) thickness of spectral-domain optical coherence tomography in the three clusters.

Variables	Cluster 1 ($n = 47$)	Group 2 ($n = 48$)	Group 3 ($n = 58$)	Overall $P^{\dagger}$	Post hoc P*		
					1 vs. 2	1 vs. 3	2 vs. 3
Average RNFL thickness (mm)	90.15 ± 7.24	72.08 ± 10.91	74.76 ± 7.03	0.012	<0.001	<0.001	0.326
Rim area (mm^2)	1.14 ± 0.15	0.72 ± 0.15	0.77 ± 0.10	<0.001	<0.001	<0.001	0.330
Disc area (mm^2)	2.37 ± 0.39	2.47 ± 0.47	1.74 ± 0.32	<0.001	0.695	<0.001	<0.001
Average C/D ratio	0.67 ± 0.06	0.83 ± 0.03	0.73 ± 0.07	<0.001	<0.001	0.081	<0.001
Vertical C/D ratio	0.67 ± 0.06	0.81 ± 0.04	0.72 ± 0.09	<0.001	<0.001	0.001	<0.001
Cup volume (mm^3)	0.41 ± 0.21	0.83 ± 0.24	0.37 ± 0.13	<0.001	<0.001	0.872	<0.001

Data are expressed as mean ± standard deviation (SD).

RNFL retinal nerve fiver layer, *C/D ratio* cup to disc ratio

*P value by Bonferroni correction for multiple testing between two clusters.

†P value by analysis of variance (ANOVA) among the three clusters.

To enable calculation of a statistically significant MD slope, each patient had to have at least five reliable VF results (excluding the first two tests) for 5 years or more during the follow-up period. A progression analysis included at least five VF tests for each patient.

Statistical analysis

Statistical analyses in this study were performed based on the clusters classified by HCA 5 years ago [3]. One-way ANOVA was used to analyse differences between clusters, and Bonferroni post-hoc test was performed to assess statistical significance between clusters. The progressive rate distribution of each cluster is represented by a histogram. All statistical analyses were conducted using SPSS software version 23.0 (SPSS, Inc, Chicago, Illinois, USA). P values < 0.05 were considered statistically significant.

Results

Among the 200 baseline patients, 153 patients satisfied our inclusion criteria after 5 years. Simple cataract surgery was performed in four eyes of cluster 1, two eyes of cluster 2, and three eyes of cluster 3. Glaucoma surgery or other intraocular surgeries were not performed. The number of patients fell from 200 to 153, their overall characteristics were the same as before. Significant differences in major points were still observed despite the reduction in sample size at follow-up.

Cluster 1 comprised 47 eyes, had the greatest average RNFL thickness (90.15 ± 7.24 mm), and had the widest rim area ($P < 0.001$). In total, 48 eyes of cluster 2 had the largest average C/D ratio (0.83 ± 0.03), vertical C/D ratio (0.81 ± 0.04) ($P < 0.001$) and largest cup volume (0.83 ± 0.24 mm^3) ($P < 0.001$). Cluster 3 contained 58 eyes and had the smallest disc area (1.74 ± 0.32 mm^2), but the other parameters had intermediate values between those of cluster 1 and 2 (Table 1).

The age of patients in cluster 1 was 56.66 ± 16.59 years, cluster 2 was 53.88 ± 14.50 years. There was no significant difference in age of patients between the two clusters. However, cluster 3 patients were 47.69 ± 15.98 years old, comprising the youngest age group ($P = 0.012$; Table 2). Sex was not significantly different among clusters. CCT was 522.59 ± 34.14 mm in cluster 2, which was thinner than that in cluster 1 ($P < 0.003$) and cluster 3 ($P < 0.015$). Axial length was significantly longer in cluster 3 (25.53 ± 1.94 mm) than in cluster 1 (24.18 ± 1.66 mm) and cluster 2 (24.69 ± 1.64 mm) ($P = 0.001$). The refractive error of cluster 3 showed the most severe myopia (−4.47 ± 3.99 D) and the cluster 2 was −2.25 ± 3.64 D, cluster 1 was nearly emmetropia, with refractive error of −0.54 ± 2.98 D ($P < 0.001$). Baseline MD was significantly lower in cluster 2 than in cluster 1 (−7.23 ± 5.71 vs. −3.19 ± 4.13 dB, $P < 0.001$). Cluster 3 showed an intermediate value (−5.25 ± 4.40 dB) that was not significantly different to those of other clusters. VFI in cluster 1 was 95.92 ± 3.96%, which was higher than that in cluster 2 and 3 ($P = 0.008$).

Cluster 1 exhibited the fastest progression rate on OCT, with a decrease in average RNFL thickness of −0.83 ± 0.89 μm/year. The progression rates for cluster 2 and 3 were −0.45 ± 0.76 μm/year and −0.36 ± 0.79 μm/year, respectively ($P < 0.011$; Table 3). The progression rate of superior and inferior RNFL thickness also demonstrated a similar pattern. Comparing the MD of VF tests, cluster 1 was significantly changed (−0.16 ± 0.61 dB/year) compared with cluster 2 (0.08 ± 0.34 dB/year, $P = 0.048$) and cluster 3 (0.11 ± 0.43 dB/year, $P = 0.017$). No significant differences among clusters in the PSD were observed.

Baseline IOP of was 15.95 ± 2.88 mmHg for cluster 1, 15.83 ± 2.80 mmHg for cluster 2, and 16.37 ± 3.02 mmHg for cluster 3, with no significant differences among groups ($P = 0.472$, Table 3). The mean IOP during the follow-up period

Table 2 Comparisons of age, sex, CCT, AL, refractive error and visual field parameters among the three clusters.

Variables	Cluster 1 ($n = 47$)	Group 2 ($n = 48$)	Group 3 ($n = 58$)	Overall $P^{\dagger}$	Post hoc P*		
					1 vs. 2	1 vs. 3	2 vs. 3
Age (mean ± SD) (year)	56.66 ± 16.59	53.88 ± 14.50	47.69 ± 15.98	0.012	>0.999	0.013	0.137
Sex (female/male)	30/17	23/25	33/25	0.296	0.362	>0.999	>0.999
CCT (mm)	544.04 ± 28.15	522.59 ± 34.14	539.72 ± 28.91	0.002	0.003	>0.999	0.015
AL (mm)	24.18 ± 1.66	24.69 ± 1.64	25.53 ± 1.94	0.001	0.493	0.001	0.056
Refractive error (D)	−0.54 ± 2.98	−2.25 ± 3.64	−4.47 ± .3.99	<0.001	0.066	< 0.001	0.006
MD (dB)	−3.19 ± 4.13	−7.23 ± 5.71	−5.25 ± 4.40	<0.001	<0.001	0.106	0.090
VFI (%)	95.92 ± 3.96‘	85.32 ± 15.38	88.43 ± 12.98	0.008	0.009	0.054	>0.999

Data are expressed as mean ± SD.

CCT central corneal thickness, *AL* axial length, *D* dioptres, MD = mean deviation, *VFI* visual field index

*P value by Bonferroni correction for multiple testing between two clusters.

†P value by analysis of variance (ANOVA) among the three clusters.

Table 3 Comparisons of optical coherence tomography, visual field progression rate and intra-ocular pressure distribution (IOP) in the three clusters.

	Cluster 1 ($n = 47$)	Group 2 ($n = 48$)	Group 3 ($n = 58$)	Overall $P^{\dagger}$	Post hoc P*		
					1 vs. 2	1 vs. 3	2 vs. 3
Rate of change							
Average RNFL thickness (μm/year)	−0.83 ± 0.89	−0.45 ± 0.76	−0.36 ± 0.79	0.011	0.068	0.011	>0.999
Superior RNFL thickness (μm/year)	−1.01 ± 1.66	−0.76 ± 1.34	−0.75 ± 1.48	0.658	>0.999	>0.999	>0.999
Inferior RNFL thickness (μm/year)	−1.12 ± 1.43	−0.69 ± 1.42	−0.59 ± 1.01	0.125	0.377	0.150	>0.999
MD (dB/year)	−0.16 ± 0.61	0.08 ± 0.34	0.11 ± 0.43	0.013	0.048	0.017	>0.999
PSD (dB/year)	0.11 ± 0.29	−0.02 ± 0.25	0.12 ± 0.34	0.048	0.143.	>0.999	0.065
IOP change							
Baseline IOP (mmHg)	15.95 ± 2.88	15.83 ± 2.80	16.37 ± 3.02	0.472	>0.999	>0.999	0.741
Mean IOP (mmHg)	12.75 ± 2.19	12.93 ± 1.47	13.36 ± 1.63	0.197	>0.999	0.250	0.671
IOP fluctuation (mmHg)	1.25 ± 0.42	1.43 ± 0.57	1.46 ± 0.64	0.129	0.376	0.160	>0.999
Count of Topical drugs	1.21 ± 0.83	1.90 ± 0.78	1.76 ± 0.94	< 0.001	<0.001	0.005	>0.999

Data are expressed as mean ± SD.

RNFL retinal nerve fibre layer, *MD* mean deviation, *PSD* pattern standard deviation, *IOP* intra ocular pressure

*P value by Bonferroni correction for multiple testing between two clusters.

†P value by analysis of variance (ANOVA) among the three clusters.

was not significantly different among cluster 1 (12.75 ± 2.19 mmHg), cluster 2 (12.93 ± 1.47 mmHg), or cluster 3 (13.36 ± 1.63 mmHg) ($P = 0.197$). IOP fluctuations were not significantly different among clusters ($P = 0.129$). The mean number of IOP lowering agents was significantly lower in cluster 1 (1.21 ± 0.83) than in cluster 2 (1.90 ± 0.78, $P < 0.001$) and cluster 3 (1.76 ± 0.94, $P = 0.005$).

Figure 1 shows the distribution of the average RNFL thickness progression rate for each cluster. Cluster 1, which progressed the fastest, was skewed toward the negative progression rate section. Cluster 2 exhibited a normal distribution with many patients falling in the range of 0 to −1.0 μm. Cluster 3 displayed a double-peak distribution.

Patients in cluster 3 were divided into two groups at −0.25 μm/year, which was the median value, and their characteristics were compared. There was no significant difference except for the rate of OCT progression between these groups ($P < 0.001$) (Table 4). The rate of RNFL thickness changes in 26 progressive patients was −0.93 ± 0.52 μm/year, similar to that in cluster 1. The other 27

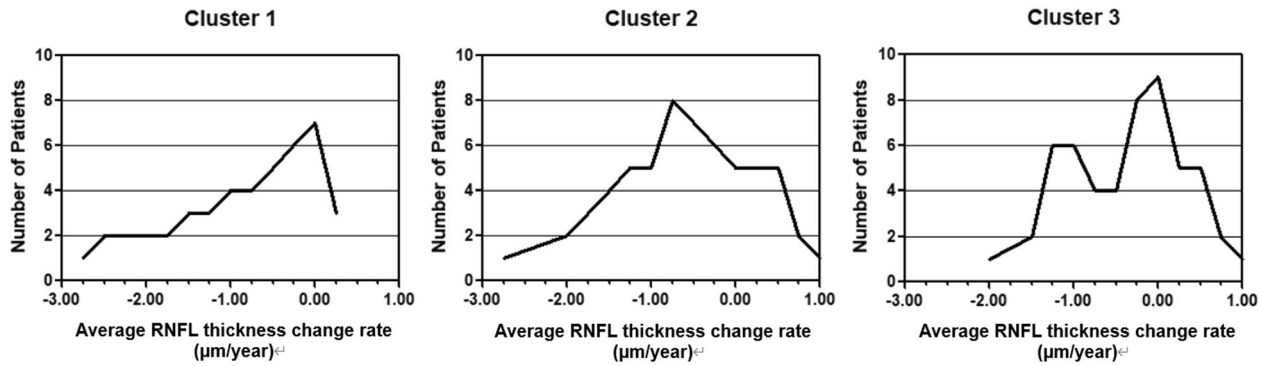

Fig. 1 Histogram illustrating the distribution of the average retinal nerve fiber layer (RNFL) thickness change rate (μm/year) identified using OCT. Cluster 1 ($n = 47$) showed the fastest progression rate. Cluster 2 ($n = 48$) showed a normal distribution with many patients falling in the range of 0 to −1.0 μm. Cluster 3 ($n = 58$) showed a double-peak distribution.

Table 4 Comparison of the characteristics of the two groups obtained from cluster 3.

Variables	Progression ($n = 28$)	Non-progression ($n = 30$)	P value*
Baseline average RNFL thickness (μm)	73.88 ± 5.13	74.75 ± 8.16	0.649
Baseline average C/D ratio	0.72 ± 0.09	0.73 ± 0.06	0.699
Baseline MD (dB)	−4.73 ± 3.86	−5.53 ± 4.39	0.487
Age (mean ± SD) (year)	47.92 ± 15.96	47.11 ± 14.71	0.848
AL (mm)	25.09 ± 1.66	25.94 ± 2.23	0.126
Refractive error (D)	−4.11 ± 3.52	−4.93 ± 4.63	0.483
Rate of RNFL thickness change (μm/year)	−0.95 ± 0.41	0.18 ± 0.33	<0.001
Rate of MD change (dB/year)	0.12 ± 0.40	0.07 ± 0.40	0.665
Baseline IOP (mmHg)	15.04 ± 1.90	14.79 ± 1.89	0.629
Mean IOP (mmHg)	13.70 ± 1.44	13.10 ± 1.79	0.180

RNFL retinal nerve fibre layer, *C/D ratio* cup to disc ratio, *MD* mean deviation, *SD* standard deviation, *AL* axial length, *D* dioptre, *IOP* intra ocular pressure

*Independent t-test, significance at $P < 0.05$.

patients showed a positive change rate of 0.20 ± 0.74 μm/year and almost no progression.

Discussion

We classified NTG using HCA in previous studies to probe the heterogeneity of NTG; from this, three groups were defined [3]. Cluster 1, which was considered as early glaucoma because of its small cup volume (0.41 ± 0.21 mm^3), large rim area (1.14 ± 0.15 mm^2) and thick RNFL thickness (90.15 ± 7.24 mm) in the baseline study. Cluster 2, which was considered as moderate glaucoma due to the large cup volume (0.83 ± 0.24 mm^3), small rim area (0.72 ± 0.15 mm^2) and thin RNFL thickness (72.08 ± 10.91 mm). Despite the small cup volume (0.37 ± 0.13 mm^3), cluster 3 showed a small rim area (0.77 ± 0.10 mm^2), due to the small disc area (1.74 ± 0.32 mm^2) from the myopic change. As a result, the RNFL thickness was thin (74.76 ± 7.03 mm) (Table 1). The baseline demographics of those in cluster 3 showed that they were still younger than those in the other groups even after the number of patients followed-up decreased, there were still several myopia patients, and AL was also the longest. The average visual field MD of cluster 2 patients was −7.23 ± 5.71 dB, which was more advanced than those of the other groups, and the VFI was also the most advanced with 85.32 ± 15.38% (Table 2). The mean ONH characteristic, age, sex, CCT, AL, refractive error, and VF parameters of each cluster did not change much compared with the baseline study, performed 5 years ago [3]. However, there was a difference in the actual progression rate of glaucoma. After 5 years of glaucoma, the stage of cluster 2 was still worse than that of cluster 1. However, cluster 1 exhibited a faster progression rate, as there was a higher prevalence of early stage glaucoma in cluster 1. Cluster 3 progressed at a similar rate to that of cluster 2. To the best of our knowledge, there have been no studies of OCT progression rate based on glaucoma stage to date. In our study, the progression rate was faster in the early stage than in the moderate stage under similar conditions.

Various factors are involved in the progression of NTG, including IOP, optic disc haemorrhage, tilt and myopia. The

extent to which these factors affect NTG progression is equivocal [7–11]. The rate and pattern of progression are inconsistent, and individual differences exist [12–14].

Most studies comparing glaucoma progression have typically employed the VF test [15–17]. In this study, despite the significantly different progression rate in VF tests among the three clusters, cluster 1 had the fastest progression rate (−0.16 ± 0.61 dB/year) of the three clusters, but progress was not meaningful. Clinically, there was no significant progression difference among the three clusters in VF tests. This is probably due to the fact that the majority of patients enroled in this study were at an early to moderate stage, and structural abnormalities in OCT were preceded by functional abnormalities in the VF test [18–20]. In early to moderate glaucoma, glaucomatous changes are typically detected in OCT before VF defects occur [17, 21–23]. All patients in this study were managed well with IOP-lowering drugs; it was challenging to identify progression cases in the VF test for 5 years. For these reasons, we focused on structural changes in OCT only, but we plan to compare functional changes in VF tests in a long-term follow-up study.

In the baseline, average RNFL thickness of cluster 1 was 90.15 ± 7.24 mm, cluster 2 was 72.08 ± 10.91 mm and cluster 3 was 74.76 ± 7.03 mm. The average rate of change in RNFL thickness was −0.83 ± 0.89 μm/year in cluster 1, which was the fastest, while those of cluster 2 and cluster 3 were similar (−0.45 ± 0.76 μm/year, −0.36 ± 0.79 μm/year) (Table 3). The reason for the rapid speed of progression in cluster 1 was that glaucoma actually progressed fast and that was reflected in the OCT. However, at the baseline, the RNFL thickness of cluster 1 was thicker than that of other clusters, and therefore the RNFL change might have been more sensitively detected in the OCT. As glaucoma progresses, the rate of RNFL thickness decrease slows down gradually, and that change is not properly reflected on the OCT [24–27]. Mean IOP was not significantly different during follow-up, as all three clusters received treatment according to the same guidelines by one glaucoma specialist. IOP decreased by approximately 20% from baseline based on the basic principles of IOP management [28–30]. Less agents were used (1.21 ± 0.83) in cluster 1, In contrast, patients were administered more topical drugs (1.90 ± 0.78) in cluster 2. This may at least partly explain why cluster 2 progressed less than cluster 1.

We predicted that cluster 3, which was myopic glaucoma NTG, would not progress or would progress differently from normal NTG during the baseline study 5 years ago [3]. However, there was no significant difference in progression rates between clusters 2 and 3. We thus analysed the progression rate as a histogram to further analyse cluster 3. The distribution of progression in cluster 3 (Fig. 1) exhibited a double-peak pattern unlike other clusters, suggesting a mixture of two different groups. Among them, one group showed rapid progression similar to that of cluster 1, and the other group hardly progressed. These two groups differed from cluster 3; however, they did not show any significant differences in baseline data or in the rate of visual field MD change except only in the rate of RNFL thickness change in OCT (Table 4). Representative cases of these two groups were compared. The two patients had similar refractive errors, ONH tilt, and peripapillary atrophy (PPA), but showed differences in the progression rate. Glaucomatous damage progressed in both the superior and inferior RNFL of the patient with the fast progression; and in the patient with the slow progression, the damage in the inferior RNFL was rarely changed for 5 years (Supplementary Fig. 2).

Myopia is a risk factor for glaucoma onset [31], but there has been widespread controversy on glaucoma progression. One opinion is that it progresses regardless of the degree of myopia or that it progresses less than other glaucoma without myopia [10, 32]. However, in this study, the progression of myopic glaucoma did not exhibit a single tendency, suggesting the presence of at least two groups with different characteristics: ‘progress’ and ‘non-progress’. In the progress group, myopia may have occurred coincidentally with glaucoma, or myopia may have increased glaucoma susceptibility. This group was likely to demonstrate glaucoma progression regardless of myopia. Conversely, myopia may have affected glaucoma onset in the non-progress group, but glaucoma progression ceased as myopia development stopped. Jonas et al. reported elongation and thinning of the sclera at the parapapillary area in highly myopic eyes. Structural changes of the sclera in myopia increase stress and strain on the lamina cribrosa, thereby increasing glaucoma susceptibility [33]. From this theory, it can be assumed that glaucoma was caused by structural changes around the ONH with the occurrence of myopia, but the progression of glaucoma would cease when myopia ceased. In conclusion, glaucoma with myopia cannot be interpreted as a single disease entity.

There are several limitations of this study. First, as this was a retrospective study, the influence of recall bias on the results must be considered. However, since this study was conducted on 200 patients previously studied, selection bias was minimised due to the observational nature of the study. Second, our results do not represent all open angle glaucoma patients because only NTG patients in South Korea were included. Third, since this was a follow-up study, follow-up loss and reduction in sample size were unavoidable; 153 eyes were a relatively small sample size. Further follow-up studies that recruit more patients with similar conditions are necessary. Fourth, this study examined the progression under treatment for more than 5 years and did not assess the natural course of NTG. Finally, although there were no significant differences in IOP parameters

among groups, the use of medication was not adjusted in this study. Thus, the effects of medication cannot be completely ruled out.

In summary, Cluster 1 which represent the early glaucoma, showed fast progression in this study. Early glaucoma is not usually treated or is tested less because there was no severe damage, but early glaucoma with low C/D ratio can progress faster. Therefore, it will be necessary to provide aggressive treatment with regular examinations. In the group with young and myopic eyes, two types of progression patterns seemed to be exhibited, and in such a group, progressive cases should be actively identified and treated. This is the first follow-up study of for more than 5 years on the progression of three NTG groups defined by HCA that demonstrated different patterns of progression. These results provide insight into the mechanisms underscoring the pathophysiology and progression of NTG.

Summary

What was known before

- In preliminary our study, NTG was classified into three groups by ONH shape.

What this study adds

- 5 years follow-up study was made to determine the difference of progression patterns between these three groups.

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Compliance with ethical standards

Conflict of interest No conflicting relationships exist for any author. The authors alone are responsible for the content and writing of the paper.

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