Baseline Thickness of Macular Ganglion Cell Complex Predicts Progression of Visual Field Loss

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Abstract

Background: Previous studies reported that the thickness of the macular ganglion cell complex (mGCC) showed good diagnostic ability for detecting glaucoma. However, its impact on the progression of visual field loss in primary open angle glaucoma (POAG) is unknown. The purpose of this study was to assess whether baseline mGCC thickness is associated with the progression of visual field loss in POAG.

Methods: Fifty-six patients with POAG were included in the study. All patients were followed for more than 2 years after baseline optical coherence tomography (OCT) measurements. They had at least 5 reliable Humphrey visual field tests with 30-2 Swedish Interactive Threshold Algorithm standard tests during the follow-up period. The subjects were divided into two groups according to the slope of the mean deviation (MD): the fast progression group (MD slope < −0.4 dB/y) and the slow progression group (MD slope ≥ −0.4 dB/y). Factors compared between the groups were as follows: age, baseline intraocular pressure (IOP), mean IOP during the follow-up, refraction, baseline MD, pattern standard deviation (PSD), and baseline OCT measurements.

Results: There were no significant differences between the two groups in age, baseline IOP, mean IOP during the follow-up, refraction, baseline MD or PSD, average thickness of retinal nerve fiber layer (RNFL), or disc parameters. However, the baseline mGCC thickness (average and inferior hemifield) was significantly thinner in the fast progression group than in the slow progression group (74.0 ± 7.2 μm vs. 80.3 ± 8.6μm; 68.0 ± 6.6 μm vs. 78.2 ± 11.6 μm, respectively). Moreover, global loss volume and focal loss volume, which are parameters of mGCC, showed significantly higher rates in the fast progression group than in the slow progression group. In multi-variate analysis, only mGCC thickness of the inferior hemifield was associated with disease progression (P = 0.007).

Conclusions: Baseline mGCC thickness can be predictive of progressive visual field loss in patients with POAG.

Keywords: macular ganglion cell complex, retinal nerve fiber layer, progression of visual field loss, primary open angle glaucoma

Introduction

Glaucoma is a progressive optic neuropathy characterized by the loss of retinal ganglion cells and the retinal nerve fiber layer (RNFL), with associated visual field loss [1, 2] . It is important to detect glaucoma progression early and prevent further visual filed loss because the loss of visual function cannot be reversed. Novel technology makes it possible to perform automatic measurements of the thickness of the macular ganglion cell complex (mGCC), which comprises the inner 3 layers of the retina (nerve fiber layer, ganglion cell layer, and inner plexiform layer) [3]. Since a substantial decrease in the retinal ganglion cell population can occur prior to detectable visual field deficits [4-7], the measurement of mGCC thickness is expected to be a useful method for detection of glaucoma at an earlier stage and tracking the progression of glaucoma. Previous studies have shown that mGCC and RNFL were useful in diagnosing glaucoma. [3, 8-11] Naghizadeh et al. [12] recently compared the rates of changes in different parameters, measured by a spectral-domain optical coherence tomography (OCT), between normal controls and patients with perimetric glaucoma. They reported that parameters of mGCC thickness may be more useful in detecting the early structural progression of glaucoma than RNFL thickness and disc parameters. Although some studies have reported that reduced RNFL thickness is predictive of visual field progression in patients with glaucoma or suspected glaucoma [13-15], few studies have reported the impact of mGCC thickness on visual filed progression. Therefore, we conducted this study to assess whether baseline mGCC thickness is associated with the progression of visual field loss in patients with POAG.

Materials and Methods

This study was approved by the Toho University Ohashi Medical Center Institutional Review Board (No.12-14), which followed the provisions of the Declaration of Helsinki. A retrospective review was undertaken in patients with glaucoma who underwent OCT measurements of both mGCC and RNFL thickness at our outpatient clinic of the Department of Ophthalmology, Toho University Ohashi Medical Center, Tokyo, Japan, between May 2008 and September 2009. The subjects meeting the inclusion and exclusion criteria described below were enrolled in the study.

The inclusion criteria were as follows: normal open anterior chamber angles on slit-lamp biomicroscopic and gonioscopic examinations, glaucomatous optic nerve head appearance on stereoscopic evaluation and corresponding visual field defects, best-corrected visual acuity of at least 20/25, refractive errors in the spherical equivalent not exceeding −8 or +3 diopters, and cylinder correction within 3 diopters. A visual field defect was defined as having three or more significant ($P < 0.05$) non-edge-contiguous points, with at least one point at the $P < 0.01$ level in the pattern deviation plot, along with grading outside the normal limits for the Glaucoma Hemifield test (GHT). In addition, all patients were followed for more than 2 years from the baseline OCT measurements and had at least 5 reliable Humphrey visual field tests with 30-2 Swedish Interactive Threshold Algorithm (SITA) standard tests during the follow-up period. The baseline of visual field was defined as the test that was performed within 3 months of the baseline OCT measurements.

The exclusion criteria included a history of intraocular surgery during the follow-up period and presence of other intraocular eye diseases or other diseases affecting the visual fields (e.g., pituitary lesions, demyelinating disease or diabetic retinopathy). In addition, subjects with advanced glaucoma who had an initial mean deviation (MD) under −12dB were excluded. If both eyes met the criteria, one eye was randomly selected.

Measurement of RNFL and mGCC

OCT measurements were performed with the RTVue-100 Fourier- Domain OCT (software version 4.0, Optovue Inc.,Fremont, CA), which uses a scanning laser diode to emit a scan beam with a wavelength of 840 ± 10 nm to provide images of ocular microstructures. In this study, the GCC scanning protocol was used for the mGCC thickness measurements. The GCC protocol consists of 1 horizontal line scan and 15 vertical line scans that cover a 7-mm x 7-mm region. In total, the GCC scans captured 15,000 data points within 0.6 seconds and made a 6-mm map corresponding to approximately 20 degrees on the visual field map. The mGCC thickness was measured from the internal limiting membrane to the outer inner plexiform layer boundary and 5 parameters were provided: 3 average thicknesses (overall thickness average, superior and inferior hemifield average) and 2 special pattern-based parameters [global loss volume (GLV) and focal loss volume (FLV)]. GLV measures the average amount of mGCC loss over the entire GCC map, and FLV measures the average amount of focal loss over the entire GCC map. GLV is similar to MD in visual fields and FLV is much like PSD in visual fields.

For circumpapillary RNFL thickness measurements and disc parameters, the ONH protocol was used. Using the fundus picture generated by OCT (video baseline protocol), we were able to manually trace the contour of ONH. The RNFL thickness was automatically measured at a diameter of 3.45 mm around the center of the optic disc. A total of 775 A scans were obtained at this circumference. Disc parameters were measured by the software that defines the cup plane as 150 μm above the connecting line of the retinal pigment epithelium tips. The following disc parameters were obtained: disc area, cup area, rim area, rim volume, nerve head volume, cup volume, cup/disc area ratio, cup/disc horizontal ratio, and cup/disc vertical ratio.

A trained operator obtained good quality OCT images with pupillary dilation. Images were excluded when the signal strength was <40 or segmentation errors or decentration of the measurement location were observed.

Analysis of visual filed

A Humphrey Field Analyzer (Carl Zeiss Meditec Inc. Dublin, CA) 30-2 SITA standard automated perimetry was used for the visual field test. The visual field tests were considered to be reliable when fixation losses were <20%, false-positives were <15%, and false-negative rates were <25%. The slope of mean deviation (MD) was used for the analysis of the rate of progression of the visual field defect. A linear regression analysis was performed using a Windows-based PC program, HfaFiles ver.5 (Beeline Office Co., Tokyo).

According to the Early Manifest Glaucoma Trial, the change in MD values for the treatment group and the control group (no treatment) were −0.03 dB/month (−0.36 dB/year) and −0.05 dB/month (0.6 dB/year), respectively [16]. In the Collaborative Norma-Tension Glaucoma Study, the estimated mean MD slopes for all subjects without treatment was −0.41dB/year [17]. Fukuchi et al. reported the mean MD slope in 315 Japanese patients with open angle glaucoma was −0.41 dB/y [18]. In this study, the subjects were divided into two groups according to the MD slope: Patients with an MD slope of <−0.4 dB/y were placed in the “fast progression” group, and patients with an MD slope of ≥−0.4 dB/y were placed in the “slow progression” group. Factors compared between the groups were as follows: age, baseline intraocular pressure (IOP), mean IOP during the follow-up, refraction, baseline MD, baseline PSD, mGCC thickness, RNFL thickness and disc parameters.

Statistical Analysis

Statistical analyses were performed using SPSS software version 19.0 (SPSS Inc, Chicago, IL, USA). The Mann–Whitney U-test was used to compare factors between the groups.

Differences in ratios were evaluated using the χ^2 test. For multi-variate analysis, a logistic regression model was used to identify predictive factors for progression of visual field loss. In this model, MD slope of <−0.4 dB/y was the dependent variable and the other factors were entered as covariates in a forward stepwise manner. Evaluated variables included age, gender, baseline RNFL thickness, baseline mGCC thickness, GLV, and FLV. Data were reported as mean ± SD. RNFL thickness of 16 sectors were analyzed with Bonferroni correction, and $P <$ 0.0031(0.05/16) was considered to be statistically significant. In other analyses, $P < 0.05$ was considered to be statistically significant.

Results

Table 1 shows the characteristics of the 56 patients with POAG who were included in the study. Most of the patients had an early stage of glaucoma. The averages of MD and PSD were −3.26 ± 3.0 dB and 6.94 ± 4.2, respectively. The subjects were divided into two groups according to the slope of MD. Figure 1 illustrates the distribution of the MD slope. There were 15 subjects with an MD slope of <−0.4 dB/y (the fast progression group), and there were 41 subjects with an MD slope of ≥ −0.4 dB/y (the slow progression group). Table 2 shows the baseline characteristics of these two groups. There were no significant differences between the groups in age, sex, follow-up period, refraction, baseline MD or PSD, baseline IOP, or mean IOP during the follow-up. Regarding the baseline IOP, 27 of 56 subjects were already on medical treatment and 29 were not on medical treatment. Because 22 of the 29 subjects who were not on treatment at baseline had started medical treatment during the follow-up period, the mean IOP during follow-up tended to be lower than the baseline IOP in both groups.

Regarding the OCT measurements, no significant differences were observed in the RNFL thickness between the groups. Figure 2 illustrates the RNFL thickness of the 16 sectors in the groups. The inferotemporal sectors tended to be thinner in the fast progression group than in the slow progression group; however, thicknesses were not statistically different. On the

other hand, the mGCC thickness (average and inferior hemifield) was significantly thinner in the fast progression group than in the slow progression group. Moreover, GLV and FLV, which are parameters of GCC, showed significantly higher rates in the fast progression group than in the slow progression group. Only the mGCC thickness of inferior hemifield among the aforementioned variables showed a significant difference (OR; 0.894, 95% confidence interval (CI); 0.825–0.970, $P = 0.007$).

Table 3 shows baseline disc parameters of the groups. There were no significant differences between the groups in disc area, cup area, rim area, rim volume, nerve head volume, cup volume, C/D area ratio, C/D horizontal ratio, and C/D vertical ratio measured by OCT.

In the subset analysis, the subjects were divided into two groups based on the pattern of visual field defects: those with visual field defects predominantly confined to the superior hemifield (superior hemifield defect group) and those with visual field defects predominantly confined to inferior hemifield (inferior hemifield defect group). In cases of bihemifield defect, the predominant hemifield was defined as the one that showed more points with $P < 0.05$ on a pattern deviation map. There were 36 subjects with a superior hemifield defect, and 20 with an inferior hemifield defect. Table 4 shows the results of baseline OCT measurements of the superior hemifield defect group. The mGCC thickness of the inferior hemifield was significantly thinner in the fast progression group than in the slow progression group. However, there was no significant difference between the groups in RNFL thickness. In addition, GLV showed significantly higher rate in the fast progression group than in the slow progression group. Table 5 shows the results of baseline OCT measurements of the inferior hemifield defect group. The mGCC thickness of the inferior hemifield was significantly thinner in the fast progression group than in the slow progression group.

Discussion

In this study, we demonstrated that the baseline mGCC thickness of the inferior hemifield was a prognostic factor for visual field loss in patients with POAG. Previous studies reported that thinner RNFL thickness at baseline was predictive of visual filed progression in glaucoma or suspected glaucoma [13-15]. There were significant correlations between RNFL and mGCC thickness in patients with glaucoma, particularly between supero-temporal RNFL and superior mGCC as well as infero-temporal RNFL and inferior mGCC [19]. Therefore, we expected that the baseline mGCC thickness would be associated with progression of visual field loss. Moreover, mGCC thickness may have an advantage over RNFL thickness in detecting the early structural change. Recently, Lee et al. reported that the regional assessment of macular inner retinal layer thickness was a better indicator of paracentral scotoma than RNFL parameters in patients with early glaucoma [20].

In our cohort, there were more subjects with visual field defect predominantly confined to the superior hemifield than those predominantly confined to the inferior hemifield. This may affect the significance of the difference that was seen in the mGCC thickness of the inferior hemifield between the two groups (fast progression or slow progression). However, after dividing the subjects into two groups based on their pattern of visual field defects (inferior hemifield and superior hemifield), the mGCC thickness of the inferior hemifield group was still significantly thinner in subjects with fast progression than in subjects with slow progression in the superior hemifield defect group. These results suggest that a significant loss in mGCC thickness can predict further visual field defects. On the other hand, in the inferior hemifield defect group, the mGCC thickness of the superior hemifield in subjects with fast progression was 8 μm thinner than that in subjects with slow progression, but the difference was not statistically significant. This may be because of the small number of the subjects. Besides, interestingly, the mGCC thickness of inferior hemifield was significantly thinner in subjects with fast progression than those with slow progression. We speculate that thinning mGCC can occur

not only in the hemifield, which shows significant visual field defect, but also in the other hemifield during progression of glaucoma. Takagi et al. investigated the thickness of mGCC in the normal visual field in glaucoma cases with hemifield defects, and they found that mGCC thickness in glaucoma patients was significantly less than that in normal control eyes [21]. We need further studies to investigate the reasons of the discrepancy between the superior and inferior hemifields.

Naghizadeh et al. [12] compared rates of change of different parameters measured by spectral-domain OCT (RTVue-100) between normal controls and patients with perimetric glaucoma. They reported that FLV and GLV showed significantly faster rate of progression in patients with glaucoma than in normal controls. FLV and GLV are pattern-based parameters that reflect different aspects of GCC loss. Some studies reported that FLV and GLV had higher diagnostic accuracy than average the mGCC thickness [3, 8, 10, 11]. These results suggest that pattern-based parameters are more sensitive than the average mGCC thickness, in some cases. In our cohort, GLV and FLV showed significantly higher rates in the fast progression group than in the slow progression group. However, in our multi-variate analysis, only mGCC thickness of the inferior hemifield showed a significant difference.

In the present study, the baseline RNFL thickness was not significantly different between the groups. Although the inferotemporal sectors tended to be thinner in the fast progression group than in the slow progression group, thicknesses were not statistically different. The inferotemporal section of RNFL has been reported as the section where RNFL progression was frequently detected [22, 23]. Leung et al. evaluated RNFL thickness, which they measured by time-domain OCT. They reported that the sector at seven o'clock (right eye orientation) was the most frequent location showing progression. In another study used spectral-domain OCT, Leung et al. reported that the inferotemporal meridian 2.0-mm away from the optic disc center was the most frequent location where RNFL progression was detected [24]. In terms of the baseline of RNFL thickness, although some studies reported a significantly lower baseline

inferior RNFL thickness in progressors than nonprogressors [15, 25], other studies did not [22]. It is well known that baseline disease severity is related to further glaucoma progression. We speculate that the relationships between the baseline thickness of RNFL and visual field progression may be associated the disease severity of the subjects.

Sehi et al. reported that abnormal baseline optic nerve head (ONH) topography, measured by confocal scanning laser ophthalmoscopy, was associated with further visual field progression [15]. However, the present study showed that there was no significant difference between the groups regarding the disc parameters measured by OCT. It may reflect a relatively weaker performance of the RTVue software for topographic assessment of ONH compared with RNFL thickness assessment. Rao et al. evaluated RNFL thickness and ONH parameters measured by spectral-domain OCT (RTVue-100) for glaucoma detection. They found that ONH measurements had inferior performance compared with RNFL thickness. They speculated that the ONH structure is likely to have greater variability than the RNFL, owing to, for example, the presence of tilting, sloping, crescents, and areas of parapapillary atrophy [26].

Reduction of IOP is the principle of treating glaucoma. It is well known that a high mean IOP is an unfavorable prognostic factor for visual field progression. In this study, the baseline and follow-up IOPs tended to be higher in the fast progression group than in the slow progression group, although the difference was not statistically significant. It might be partly because of the small sample size.

The present study has several limitations. First, because of the nature of the retrospective study, one half of the subjects had already been treated at the time of their baseline OCT measurements. Therefore, we were unable to identify any effect of IOP reduction on visual field conversion. Second, in this study, we divided the study population into two groups according to the MD slope. The results may differ from those with a different definition of the

progression for visual field loss. However, we compared the top 25% of subjects (average MD slope; 0.64±0.21 dB/y) and the bottom 25 % (average MD slope;-0.80±0.27 dB/y) according to the MD slope. The result showed the same trend in that the baseline mGCC of the inferior hemifield was thinner in the bottom 25% subjects than in the top 25% subjects (data not shown). Finally, we did not see any change in the OCT measurements; therefore, the rates of progression of RNFL thickness and mGCC thickness were not obtained.

In conclusion, our results demonstrate that the baseline mGCC thickness of the inferior hemifield was a prognostic factor for visual field loss in patients with POAG. Decrease in mGCC thickness can indicate further progression of visual field loss and measurement of the mGCC thickness may be a more effective method to detect early structural progression in early glaucoma than measurement of RNFL thickness.

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Table 1. Patient characteristics

	Mean ±SD
Age (y)	55.4±11.6
Sex (Male/Female)	25/31
Follow-up period (months)	32.3±6.1
Spherical equivalents (D)	−3.61±2.6
Mean deviation (dB)	−3.26±3.0
Pattern standard deviation (dB)	6.94 ±4.2
Baseline IOP(mmHg)	14.6 ±3.2

IOP, intraocular pressure

Table 2. Baseline characteristics of the defined groups

	Fast progression (MD slope < -0.4dB/y) (n = 15)	Slow progression (MD slope ≥ -0.4dB/y) (n = 41)	*P*
Age (y)	54.3 ± 12.1	55.8±11.5	0.919[a]
Sex (Male/Female)	5 / 10	21 / 20	0.303[b]
Follow-up period (months)	33.0 ± 7.1	32.1±5.7	0.746[a]
Spherical equivalents (D)	−3.6 ±2.5	−3.6 ±2.7	0.919[a]
Mean deviation (dB)	−3.4 ±3.1	−3.2 ±2.9	0.781[a]
Pattern standard deviation (dB)	8.4±4.8	6.4 ±3.8	0.186[a]
IOP (mmHg)			
Baseline	15.7±3.2	14.2 ±3.1	0.134[a]
During follow-up	14.3±1.8	13.6 ±2.2	0.160[a]
RNFL			
Average (μm)	82.2±8.9	84.1±9.2	0.360[a]
Superior hemifield (μm)	86.7±11.8	86.6±13.4	0.860[a]
Inferior hemifield (μm)	77.6±8.1	81.5±9.4	0.240[a]
mGCC			
Average (μm)	**74.0±7.2**	**80.3±8.6**	**0.017[a]**
Superior hemifield (μm)	79.9±10.1	82.4±10.4	0.471[a]
Inferior hemifield (μm)	**68.0±6.6**	**78.2±11.6**	**0.002[a]**
Global loss volume (%)	**24.2±6.5**	**18.1±7.9**	**0.008[a]**
Focal loss volume (%)	**8.9±2.5**	**6.6±3.6**	**0.023[a]**

The values written in bold are statistically significant
[a]Mann–Whitney U test
[b]Chi-square test
IOP, intraocular pressure; RNFL, retinal nerve fiber layer; mGCC, macular ganglion cell complex

Table 3. Disc parameters of the defined groups

	Fast progression (MD slope < -0.4dB/y) (n = 15)	Slow progression (MD slope≥ -0.4dB/y) (n = 41)	*P**
Disc area (mm^2)	2.136	2.324	0.390
Cup area (mm^2)	1.358	1.577	0.267
Rim area (mm^2)	0.779	0.738	0.448
Rim volume (mm^3)	0.068	0.065	0.275
Nerve head volume (mm^3)	0.136	0.126	0.267
Cup volume (mm^3)	0.402	0.500	0.219
Cup-disc area ratio	0.603	0.664	0.215
Horizontal cup-disc ratio	0.837	0.870	0.218
Vertical cup-disc ratio	0.793	0.830	0.437

*Mann–Whitney U-test

Table 4. OCT measurements of superior hemifield defect group

	Fast progression (MD slope < -0.4dB/y) (n = 12)	Slow progression (MD slope≥ -0.4dB/y) (n = 24)	*P**
RNFL			
Average (μm)	83.3 ± 9.1	85.6 ± 8.0	0.330
Superior hemifield (μm)	89.6 ± 10.9	92.3 ± 11.6	0.383
Inferior hemifield (μm)	76.9 ± 8.2	78.9 ± 7.3	0.460
mGCC			
Average (μm)	75.5 ± 6.3	80.9 ± 7.9	0.107
Superior hemifield (μm)	82.8 ± 8.3	86.8 ± 8.6	0.227
Inferior hemifield (μm)	**68.2 ± 6.5**	**75.0 ± 10.8**	**0.048**
Global loss volume (%)	**24.7 ± 5.4**	**17.4 ± 7.2**	**0.035**
Focal loss volume (%)	9.1 ± 2.3	7.0 ± 3.8	0.093

The values written in bold are statistically significant
*Mann–Whitney U-test
RNFL, retinal nerve fiber layer; mGCC, macular ganglion cell complex

Table 5. OCT measurements of inferior hemifield defect group

	Fast progression (MD slope < -0.4dB/y) (n=3)	Slow progression (MD slope ≥ -0.4dB/y) (n=17)	*P**
RNFL			
Average (μm)	78.0 ± 8.5	81.9 ± 10.6	0.491
Superior hemifield (μm)	75.3 ± 8.9	78.6 ± 11.9	0.427
Inferior hemifield (μm)	80.6 ± 8.1	85.2 ± 11.1	0.634
mGCC			
Average (μm)	67.6 ± 8.1	79.5 ± 9.8	0.081
Superior hemifield (μm)	68.2 ± 9.3	76.2 ± 9.7	0.186
Inferior hemifield (μm)	**67.1 ± 8.2**	**82.8 ± 11.6**	**0.039**
Global loss volume (%)	30.0 ± 8.2	19.0 ± 9.0	0.081
Focal loss volume (%)	8.5 ± 3.5	6.1 ± 3.2	0.153

The values written in bold are statistically significant
*Mann–Whitney U-test
RNFL, retinal nerve fiber layer; mGCC, macular ganglion cell complex

Figure legend

Fig 1. Distribution of MD slope

MD, mean deviation

Fig 2. RNFL thickness of 16 sectors

* Statistically significant
RNFL, retinal nerve fiber; TU, temporal upper sector; ST, superotemporal sector;
SN, superonasal sector; NU, nasal upper sector; NL, nasal lower sector;
IN, inferonasal sector; IT, inferotempral sector; TL, temporal lower sector

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