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Microstructure of Peripapillary Atrophy and Subsequent Visual Field Progression in Treated Primary Open-Angle Glaucoma

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Purpose: To investigate the relationship between the microstructure of β-zone peripapillary atrophy (PPA) and the subsequent visual field (VF) progression in eyes with primary open-angle glaucoma (POAG), including highly myopic eyes.

Design: Retrospective cohort study.

Participants: A total of 129 patients with POAG who had been followed up for a minimum of 2 years and had undergone at least 5 reliable standard automated perimetry tests after spectral-domain (SD) optical coherence tomography (OCT) examination.

Methods: β-Zone PPA was evaluated from 3 SD OCT scans centered on the optic disc. Upper and lower scans were defined as scans at 30° above and below the horizontal scan, respectively. From 3 scans of each eye, β-zone PPA was classified as PPA_{+BM} or PPA_{-BM} on the basis of the presence or absence of Bruch's membrane (BM), respectively. Eyes were classified into 3 groups according to the horizontal scan images: group A (only PPA_{+BM}), group B (both PPA_{+BM} and PPA_{-BM}), and group C (only PPA_{-BM}). Factors associated with the subsequent mean deviation (MD) slope after OCT examination were analyzed, and the hemifield total deviation (TD) slope was assessed in eyes with unilateral hemifield VF defects in the corresponding direction.

Main Outcome Measures: Subsequent MD slope after OCT examination.

Results: The VF progression in group A was faster than in group C ($P = 0.004$). A larger PPA_{+BM} width was associated with a faster MD slope in all eyes ($P < 0.001$) and highly myopic eyes ($P < 0.001$) and with a faster TD slope in eyes with superior or inferior hemifield VF defects in the corresponding direction ($P = 0.002$ and $P = 0.035$, respectively). A larger PPA_{-BM} was correlated with a slower MD slope in all eyes ($P = 0.030$ and $P = 0.034$) but not in highly myopic eyes.

Conclusions: There were significant differences in VF progression according to the microstructure of the β-zone PPA in eyes with POAG. The PPA_{+BM} width may be an important risk factor for VF progression in POAG, including high myopia, and the PPA_{-BM} width may have a protective effect for VF progression in this subtype of POAG. *Ophthalmology 2015;■:1–10 © 2015 by the American Academy of Ophthalmology.*

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Peripapillary atrophy (PPA) can be subdivided into α-zone and β-zone subtypes.[1] The α-zone PPA is characterized by irregular hypopigmentation and hyperpigmentation of the retinal pigment epithelium, located in the periphery of the PPA. The β-zone PPA is characterized by atrophy of the retinal pigment epithelium and choriocapillaries, visible sclera, and large choroidal vessels, located between the optic disc and the α-zone.[1,2] Several previous studies have shown that β-zone PPA is associated with the incidence and progression of glaucoma.[1–8] Peripapillary atrophy also has been commonly reported in highly myopic eyes;[9–11] however, the relationship between PPAs in glaucoma and myopia is not fully understood.

Jonas et al[12] histologically subdivided classic β-zone PPA into newly defined β-zone PPA existing with Bruch's membrane (BM) (PPA_{+BM}) and newly defined γ-zone PPA containing no overlying BM (PPA_{-BM}). This showed that PPA_{+BM} is associated with glaucoma but not with myopia, whereas PPA_{-BM} is unrelated to glaucoma but related to myopia. However, the authors of this histologic study reported several potential limitations, such as measurement deviations in tissue preparation, sampling bias, and insufficient clinical data.

Recent studies have demonstrated that BM opening is easily detectable using spectral-domain optical coherence tomography (SD OCT).[13–17] The PPA_{+BM}, but not

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PPA_{-BM}, was found to be associated with the presence of glaucoma using SD OCT;[15] this was consistent with the findings of the previous histologic study.[12] Kim et al[13] demonstrated that glaucomatous eyes exhibiting only PPA_{+BM} demonstrate a faster rate of retinal nerve fiber layer thinning than eyes with PPA_{-BM} only. This suggests that the presence of PPA_{+BM} may be a risk factor for progressive glaucomatous visual field (VF) defects. However, it has not been validated whether the progression of glaucomatous VF defects varies according to different microstructures of the β-zone PPA. Furthermore, it is unknown whether PPA_{+BM} in highly myopic eyes is associated with the presence or progression of glaucoma, as reported in nonhighly myopic eyes.

In the current study, we investigated the relationship between the microstructure of β-zone PPA and the subsequent VF progression to determine the potential of β-zone PPA microstructure as a predictive factor for future glaucoma progression in glaucomatous eyes, including highly myopic eyes.

Methods

Subjects

Subjects examined by radial scans of the optic disc using an SD OCT system (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) at the glaucoma service in Kyoto University Hospital between November 5, 2007, and June 15, 2012, were candidates for this retrospective cohort study. The study and data collection adhered to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine. All participants consented to the ophthalmic examinations before they were performed.

All subjects in the database had already undergone a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA) measurement (5 m Landolt chart), refraction, keratometry, slit-lamp examination, axial length measurement (IOLMaster 500, Carl Zeiss Meditec, Dublin, CA), central corneal thickness (SP-3000, Tomay, Tokyo, Japan), optic disc size on clinical examination (Heidelberg Retina Tomography 2, Heidelberg Engineering), Goldmann applanation tonometry, gonioscopy, indirect ophthalmoscopy, dilated slit-lamp optic nerve head examination, fundus photography, stereo disc photography (3-Dx simultaneous stereo disc camera, Nidek, Gamagori, Japan), red-free fundus photography (Heidelberg Retina Angiography 2, Heidelberg Engineering), standard automated perimetry (SAP) (Humphrey Visual Field Analyzer, Carl Zeiss Meditec) with the 24-2 Swedish Interactive Threshold Algorithm standard program, and SD OCT. The baseline intraocular pressure (IOP) was defined as the average of the 2 measurements obtained on the first day and at the following SD OCT examination date. Mean IOP measurements were obtained by averaging all IOP measurements during follow-up, and IOP fluctuation was determined using the standard deviation of these values.

We only included subjects with primary open-angle glaucoma (POAG) who had been followed up for at least 2 years and had undergone at least 5 reliable SAP tests after the SD OCT examination date. Primary open-angle glaucoma was defined as the presence of a normal anterior chamber on slit-lamp, normal open angle on gonioscopy, glaucomatous appearance of the optic disc, or retinal nerve fiber layer defects that corresponded with typical reproducible VF defects on SAP, as confirmed by 2 reliable consecutive tests. We excluded those with opaque media, diabetic retinopathy, or other ophthalmic diseases that could cause VF defects or fundus abnormalities, history of eye trauma or intraocular surgery other than cataract and glaucoma surgery, history of systemic or neurologic diseases that can affect the VF, and those with a BCVA <20/40. If subjects underwent cataract or glaucoma surgery during follow-up, we included only those who met the inclusion criterion before surgery. When both eyes of a subject were eligible, 1 eye was randomly selected for the study. In this study, high myopia was defined by an axial length exceeding 26 mm.

Visual Field Assessment

The criteria of Anderson and Patella[18] was used to define glaucomatous VF results on SAP: glaucoma hemifield test outside normal limits, pattern standard deviation probability <5%, or a cluster of 3 or more adjacent nonedge points in typical glaucomatous locations that did not cross the horizontal meridian (all of which were depressed on the pattern deviation plot at a $P < 5\%$; 1 of which was depressed at a $P < 1\%$ level on at least 2 consecutive plots). Visual field results were considered reliable on the basis of a fixation loss ≤15%, a false-positive ≤15%, and a false-negative ≤15%.

Glaucomatous unilateral hemifield VF defects were defined as VF defects according to Anderson and Patella's criteria in the superior or inferior hemifield only.

Spectral-Domain Optical Coherence Tomography Imaging of β-Zone Peripapillary Atrophy Area

The Spectralis HRA+OCT system was used to scan the optic disc including the PPA before the sequence of SAP tests. Tomographic images of the optic disc were obtained with infrared (IR) fundus images acquired simultaneously using a confocal scanning laser ophthalmoscope. Our disc scan protocol comprised 6 raster scan lines with a scan length of 6 mm centered on the optic disc (not based on BM opening), and the B-scan image on each scan line was obtained by averaging 50 scans. This study obtained 3 B-scans: horizontal scans and upper and lower scans that were defined as scans 30° above and below the horizontal scan, respectively (Fig 1).

β-Zone Peripapillary Atrophy Area Measurements

The structure of the temporal β-zone PPA and optic disc was analyzed with the intrinsic viewer (Heidelberg Eye Explorer software version 1.7.0.0; Heidelberg Engineering). This viewer automatically synchronizes the vertical lines of each B-scan and IR image. The distance between 2 arbitrary points, measured with intrinsic calipers, was used to correct for the effect of corneal curvature. The temporal β-zone PPA margin, BM opening, and disc margin were defined using IR and B-scan images magnified to 200% by the first examiner (H.Y.), in a masked fashion. The temporal disc margin and β-zone PPA margin was defined as the border between low and high reflectivity on IR images. The BM opening was identified on optical coherence tomography (OCT) B-scans as the termination of highly reflective continuous lines (Fig 1). Eyes were excluded when these points could not be clearly identified.

On the basis of the location of BM opening within the β-zone PPA area, β-zone PPA was subdivided into PPA_{+BM}, the zone from β-zone PPA margin to BM opening, and PPA_{-BM}, the zone from BM opening to the disc margin. The widths of β-zone PPA,