In-Vivo Microstructural Anatomy of β-Zone Parapapillary Atrophy in Glaucoma

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PURPOSE. To assess the microstructural anatomy of clinical β-zone parapapillary atrophy (βPPA) by using Fourier-domain optical coherence tomography (FD-OCT).

METHODS. Color photographs and horizontal cross-sectional FD-OCT images of the optic disc and parapapillary retina were obtained in 24 eyes (24 patients with glaucoma or suspected glaucoma) with βPPA. The distances between the temporal disc margin and parapapillary landmarks (clinical βPPA margin and the edges of the retinal pigment epithelium [RPE], Bruch’s membrane [BM], and the photoreceptor inner/outer segment [IS/OS] junction) were measured in 5 equally spaced horizontal meridians (total, 120 meridians).

RESULTS. The mean age was 56 ± 13 (SD) years. In the five meridians, the mean distances from the temporal disc margin to the temporal βPPA margin and the edges of RPE, BM, and the IS/OS junction were 388 ± 173, 371 ± 174, 214 ± 204, and 502 ± 167 μm, respectively. The RPE edge corresponded to the βPPA margin in 78 (65%) of 120 meridians and ended within the βPPA in 42 (35%) of 120 meridians. The BM edge corresponded to the RPE edge in 13 (11%) of 120 meridians and was closer to the disc in 107 (89%) of 120 meridians. The disc margin corresponded to the BM edge in 20 (17%) of 120 meridians and to the edge of the border tissue of Elschnig in 100 (83%) of 120 meridians. The IS/OS junction edge was farther from the disc than the temporal βPPA margin was in all 24 eyes.

CONCLUSIONS. The βPPA was not completely denuded of RPE, and there was a crescent-shaped area of photoreceptor degeneration or atrophy peripheral to the βPPA. The termination of the border tissue of Elschnig constituted the temporal disc margin in most eyes with βPPA. (Invest Ophthalmol Vis Sci. 2010;51:6408–6413) DOI:10.1167/iovs.09-4100

Glaucoma is a progressive optic neuropathy with characteristic structural abnormalities of the optic nerve complex (optic nerve head and parapapillary retina). A variety of clinical features of the optic nerve complex, which can be evaluated by ophthalmoscope, have been attributed to glaucomatous structural damage,1–4 as well as its progression.5–7 Systematic and careful examination of the optic nerve complex should include observation of the optic disc size, distribution of the neuroretinal rim tissue, integrity of the retinal nerve fiber layer, the presence of optic disc hemorrhage, and the presence of β-zone parapapillary atrophy (βPPA).8 βPPA has received increasing attention, as several reports have demonstrated, not only its association with the presence of glaucoma,9–11 but also its enlargement as the disease worsens12,13 and its potential role as a predictor of future progression,14–17 although these results have been controversial.18–20

βPPA was initially described more than 80 years ago,21 but its pathophysiology remains a mystery. Histologic studies have helped to correlate morphologic characteristics with the ophthalmoscopic clinical findings.22–25 These studies demonstrated atrophied or degenerated outer retinal layers. However, histologic processing of enucleated or postmortem specimens may lead to the alterations of the normal architecture seen in vivo, which may affect their interpretation. Also, some subjects in these histologic studies had malignant melanoma, with or without secondary increased intraocular pressure,22,23 and others had absolute secondary angle-closure glaucoma,24 both of which differ substantially from open-angle glaucoma.

New technologies that allow rapid, high-resolution imaging of ocular structures have become available to help evaluate glaucoma and retinal diseases.26 It is now possible to obtain real-time, in vivo images of the optic nerve complex, with a resolution comparable to that in histologic analyses and to correlate them with clinical findings.27–29 Our hypothesis was that due to the aforementioned limitations of histologic studies, in vivo morphologic characterization of βPPA by high-resolution imaging should allow a more accurate description of the parapapillary microstructural anatomy in glaucoma patients. To test this hypothesis, we used Fourier-domain optical coherence tomography (FD-OCT) to obtain parapapillary microstructural images in patients with glaucoma or suspected glaucoma with βPPA and quantitatively analyzed them.

METHODS

This is a cross-sectional analysis of data obtained from an ongoing, prospective, longitudinal study approved by the New York Eye and Ear Infirmary Institutional Review Board. Written, informed consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki.

We prospectively included patients with glaucoma or suspected glaucoma. All participants had open angles by gonioscopy, best-corrected visual acuity of 20/40 or better, and refractive errors of ±3.0 diopters and less than 2.0 diopters. Each participant had simultaneous color optic disc stereophotographs (Stereo Camera Model 3-DX; Nidek Inc., Palo Alto, CA), standard automated perimetry (Humphrey Visual Field Analyzer, 24-2 SITA-Standard strategy; Carl Zeiss Meditec, Inc., Dublin, CA), and FD-OCT (3D OCT-1000; Topcon Corporation, Tokyo, Japan) imaging of the optic nerve complex in both eyes on the same day.
excluded individuals with previous posterior segment intraocular surgery, secondary causes of glaucoma (uveitis, trauma, proliferative diabetic retinopathy, or retinal vascular obstruction), systemic or ocular diseases known to affect the visual field (pituatory lesions or demyelinating diseases), inability to perform visual field examinations reliably, and optic disc images of poor quality.

Glucomatous optic disc damage was defined as neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect, or a between-eye asymmetry of the vertical cup-disc ratio >0.2. Standard automated perimetry results were considered abnormal if the pattern standard deviation was triggered at the 5%, 2%, 1%, or 0.5% levels or the glaucoma hemifield test result was outside normal limits. A perimetric abnormality required confirmation with an additional visual field test. Patients with suspected glaucoma had signs of glucomatous optic disc damage with normal visual field test results. Those with established glaucoma had optic disc damage with repeatable visual field loss.

From this database (n = 130), we further selected only patients with glaucoma or suspected glaucoma with clearly visible βPPA on good-quality optic disc photographs and high-quality FD-OCT scans (manufacturer-provided quality factor, ≥0.60). Stereophotographs were reviewed by two glaucoma specialists (SCP, CGVDM). We defined PPA as an inner crescent of chorioretinal atrophy with visible sclera and choroidal vessels (βPPA) and an outer irregular area of hypopigmentation (α-zone PPA).8,9 The βPPA had to involve at least the temporal 180° of the optic disc and have a horizontal width of ≥150 μm in at least one meridian.

FD-OCT Imaging

Through integration with a nonmydriatic retinal camera, the FD-OCT unit used in the present study provides high-resolution, cross-sectional, three-dimensional volumetric images of the posterior fundus with a black-and-white en face projection image and a color photograph of the optic disc. The system utilizes a near-infrared, low-coherence superluminescent diode (840 nm) light source with a scanning speed of 25,000 A-scans/second, achieving excellent axial (6 μm) and lateral (10 μm) resolution. The protocol acquires a set of high-definition OCT images of the optic nerve complex in a raster pattern with a scan density of 128 x 512 in ~3.6 seconds for 65,536 A-scans. For this study, horizontal cross-sectional scans of the optic nerve complex were used, and the images with manufacturer-provided quality scores greater than 60 without motion artifacts were analyzed. Quality scores range from 0 to 100, with a higher score corresponding to better image quality.

First, the en face projection image of the optic disc was aligned with the color optic disc photograph by manual overlay, in a manner described elsewhere (Fig. 1).35 With the resultant margins of the optic disc and βPPA in the en face projection image corresponding well with those in the color disc photograph in all eyes. This alignment involved zoom and/or rotation of the color disc photographs. The optic disc margin in clinical color disc photographs was delineated as has been published.31,32 The disc border was defined as the inner edge of the scleral ring of Elschnig. When a reflective structure was absent, the observer selected the termination of pigment as the disc margin. The FD-OCT provided simultaneous visualization of the en face projection image and the two-dimensional, horizontal, cross-sectional image of the optic nerve complex, as well as direct, real-time correlation between these two images (Figs. 2–4). The outer retinal layers, including the photoreceptor inner segment/outer segment (IS/OS) junction and the retinal pigment epithelium (RPE), Bruch’s membrane (BM), and border tissue of Elschnig, were identifiable in the temporal parapapillary area.33 The RPE could not be easily distinguished from BM outside the parapapillary area, but the edge of the RPE were identified as a steplike structure (Figs. 2C, 3C, 4C).

The measurements were performed with OCT mapping software (3D OCT-1000 TrueMap Software; ver. 2.1; Topcon Corporation). The distances from the temporal optic disc margin in en face projection images to the following temporal parapapillary microstructures were measured in the horizontal cross-sectional FD-OCT scans: (1) the temporal margin of clinical βPPA, (2) the edge of the RPE, (3) the edge of BM, and (4) the edge of the photoreceptor IS/OS junction. All images were measured and analyzed in a masked fashion by two observers. To evaluate the reproducibility of measurements, we initially performed a trial using a different set of 17 FD-OCT images of the optic nerve complex, in which the two investigators independently measured the same described parameters. The interinvestigator reproducibility determined by intraclass correlation coefficients (ICCs) was excellent for all parameters (r = 0.78–0.99). After the method was validated, five horizontal, cross-sectional FD-OCT scans of the optic disc complex, which were equally spaced within the vertical diameter of the optic disc (Fig. 2A), were obtained from each eye, and the described parameters were measured from each cross-sectional scan by the two investigators together. When the two investigators disagreed on the disc margin or the parapapillary microstructures, a mutual conclusion was reached after a discussion. When the edges of the microstructures were not clearly visualized, an adjacent horizontal cross-sectional FD-OCT scan, approximately 47 μm apart from the original meridian, was used for measurement. The Topcon 3D OCT-1000 provides 128 horizontal cross-sectional scans within 6 mm, with each B-scan approximately 47 μm apart from the adjacent one. The level of significance was P < 0.05 (two-sided) for all statistical tests (SPSS, ver. 11.0; SPSS, Chicago, IL).

RESULTS

A total of 24 eyes (24 subjects) with clearly visible βPPA met the entry criteria. The mean (±SD) age was 56 ± 13 years (range, 27–76), and there were 7 subjects of African descent, 13 of European descent, and 4 of Asian descent. One subject had a history of uncomplicated cataract surgery, and another had undergone uncomplicated combined cataract surgery and trabeculectomy with mitomycin C. The baseline characteristics of the subjects are shown in Table 1.

Among a total of 120 horizontal cross-sectional FD-OCT scans, approximately 47% (56 scans) showed an unclear edge of one or more parapapillary microstructures, so an adjacent scan was used for measurement, as described in the Methods section. The mean distances between the temporal optic disc margin and the temporal margin of clinical βPPA, the edge of the RPE, the edge of BM, and the edge of the photoreceptor IS/OS junction (ΔβPPA, ΔRPE, ΔBM, and ΔIS/OS, respectively) at five equally spaced horizontal meridians crossing the optic disc are shown in Table 2. Mean horizontal and vertical optic

FIGURE 1. An en face projection image of optic disc and parapapillary retina aligned with color optic disc photograph by manual overlay.

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Disc diameters were 1391 ± 11006 153 (range, 1117–1637) and 1786 ± 243 (range, 1222–2162) μm, respectively. The mean RPE was significantly smaller than the mean PPA at all five meridians (all P < 0.03), which demonstrated that the clinical PPA region was not absolutely denuded of RPE. A short segment of RPE was present within the clinical PPA in 42% (10/24 eyes), 25% (6/24 eyes), 42% (10/24 eyes), 25% (6/24 eyes), and 42% (10/24 eyes) in meridians 1, 2, 3, 4, and 5, respectively (P = 0.476, by Pearson’s χ² test). Of the total 120 meridians, the BM edge was closer to the optic disc than the RPE edge in 107 (89%) and corresponded to the RPE edge in 13 (11%). The temporal optic disc margin corresponded to the edge of BM in all five meridians (Fig. 4) in 4 (17%) of 24 eyes. The superior edge of the border tissue of Elschnig was internal to the border tissue–scleral junction (internally oblique border tissue of Elschnig) in these four eyes, as described in other reports. In the remaining 20 eyes (100/120 meridians; 83%), the temporal optic disc margin corresponded to the edge of the border tissue of Elschnig (Figs. 2, 3), and the superior edge of the border tissue of Elschnig was external to the border tissue–scleral junction (externally oblique border tissue of Elschnig) in four eyes. The termination of the externally oblique border tissue of Elschnig constitutes the temporal optic disc margin.

Mean ΔRPE was significantly smaller than the mean ΔPPA at all five meridians (all P < 0.03), which demonstrated that the clinical βPPA region was not absolutely denuded of RPE. A short segment of RPE was present within the clinical βPPA in 42% (10/24 eyes), 25% (6/24 eyes), 42% (10/24 eyes), 25% (6/24 eyes), and 42% (10/24 eyes) in meridians 1, 2, 3, 4, and 5, respectively (P = 0.476, by Pearson’s χ² test). Of the total 120 meridians, the RPE edge corresponded to the clinical temporal βPPA margin in 78 (65%; Figs. 2, 4) and was within the βPPA in 42 (35%; Fig. 3). The mean horizontal width of the RPE segment within the βPPA was 17 ± 26 μm (range, 0–115 μm).

Mean ΔBM was also significantly smaller than the mean ΔβPPA at all five meridians (P < 0.001). The mean horizontal width of the BM segment internal (proximal) to the temporal margin of βPPA toward the optic disc was 174 ± 118 μm (range, 0–534 μm). The BM edge was closer to the optic disc than the RPE edge in 96% (23/24), 88% (21/24), 83% (20/24), 88% (21/24), and 92% (22/24) of eyes in meridians 1, 2, 3, 4, and 5, respectively (P = 0.691, by Pearson’s χ² test). Of the total 120 meridians, the BM edge was closer to the optic disc than the RPE edge in 107 (89%) and corresponded to the RPE edge in 13 (11%). The temporal optic disc margin corresponded to the edge of BM in all five meridians (Fig. 4) in 4 (17%) of 24 eyes. The superior edge of the border tissue of Elschnig was internal to the border tissue–scleral junction (internally oblique border tissue of Elschnig) in these four eyes, as described in other reports. In the remaining 20 eyes (100/120 meridians; 83%), the temporal optic disc margin corresponded to the edge of the border tissue of Elschnig (Figs. 2, 3), and the superior edge of the border tissue of Elschnig was external to the border tissue–scleral junction (externally oblique border tissue of Elschnig) in four eyes.

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The mean ΔIS/OS was significantly greater than the mean ΔβPPA at all five meridians (P < 0.001), which demonstrated that there was photoreceptor degeneration or atrophy peripheral and adjacent to the βPPA as well as inside the βPPA. The photoreceptor IS/OS junction ended outside the βPPA in all 24 eyes (Figs. 2, 3, 4), and the mean horizontal width of the IS/OS junction-free area outside the temporal border of βPPA was 115 ± 59 μm (range, 0–332 μm). It was difficult to demarcate the border of BM or the photoreceptor IS/OS junction ophthalmoscopically.

**DISCUSSION**

Our FD-OCT microstructural image analysis suggests that the anatomy of the parapapillary retina including βPPA should probably be redefined to include more precise landmarks. The RPE border did not always correspond with the clinical βPPA margin, indicating that the clinical βPPA was not completely denuded of RPE. The externally oblique border tissue of Elschnig, not BM, constituted the optic disc margin in many subject eyes (83%), and the BM constituted the optic disc margin in the eyes with internally oblique border tissue of Elschnig (17%). In addition, there was an irregular, crescent-shape area of photoreceptor degeneration or atrophy peripheral and adjacent to clinical βPPA. The horizontal widths of the RPE segment inside the βPPA, the BM segment internal (proximal) to the temporal margin of βPPA toward the optic disc, and the crescent-shape area of photoreceptor degeneration or atrophy peripheral and adjacent to βPPA were highly variable.

A previous histologic investigation of PPA reported that the βPPA represents a complete loss of RPE and an incomplete loss of adjacent photoreceptors.\(^3\)\(^1\),\(^3\)\(^2\) In the present study, however, RPE was present inside the βPPA in 35% of parapapillary FD-OCT images, which indicated that the βPPA was not absolutely denuded of RPE but contained a small segment of RPE. This discrepancy can be attributed to the different nature of both studies. In the histologic study, eyes were used that had been enucleated for malignant uveal melanoma, and tissue processing after enucleation may have altered some of the histologic features of PPA. However, in vivo imaging of PPA using FD-OCT can provide a more accurate description of the microstructures of the parapapillary retina. Also, simultaneous visualization of the two-dimensional, horizontal, cross-sectional image of the optic nerve complex and the optic disc photographs and real-time correlation between these two images may make FD-OCT analysis more accurate than histologic study. The short segment of RPE found in the βPPA in our study may not have had sufficient pigment to be visible ophthalmoscopically.

Our findings regarding the temporal optic disc margin are consistent with the results of two studies performed by Strouthidis et al.\(^3\)\(^1\),\(^3\)\(^2\) using normal monkey eyes without βPPA, in that the termination of BM constituted the disc margin with internally oblique border tissue of Elschnig and the termination of border tissue of Elschnig constituted the disc margin with the externally oblique border tissue of Elschnig. Also, the BM opening was not always a clinically detectable entity, and it was especially difficult to clinically detect the BM edge in the area where the border tissue of Elschnig was externally oblique.\(^3\)\(^1\),\(^3\)\(^2\) We additionally found that, in the human eyes with obvious βPPA, the location of the edge of BM was highly variable, ranging from the peripheral border of clinical βPPA to the optic disc margin, and the edge of the externally oblique border tissue of Elschnig constituted the disc margin in most eyes (20/24, 83%). In the remaining four

**TABLE 1. Baseline Clinical Characteristics of 24 Subjects with Clearly Visible βPPA Who Had Color Photography and FD-OCT of the Optic Disc and Parapapillary Retina**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>24 (24 eyes)</td>
</tr>
<tr>
<td>Age, y(^{+}) (range)</td>
<td>56 ± 13 (27–76)</td>
</tr>
<tr>
<td>Female/male</td>
<td>12/12</td>
</tr>
<tr>
<td>Spherical equivalent, D(^{+}) (range)</td>
<td>−2.44 ± 2.62 (−5.75 to +3.00)</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg(^{+})</td>
<td>14.7 ± 2.7</td>
</tr>
<tr>
<td>Visual field mean deviation, dB(^{+})</td>
<td>−4.55 ± 5.77</td>
</tr>
<tr>
<td>Diagnosis, n</td>
<td></td>
</tr>
<tr>
<td>Suspected glaucoma</td>
<td>8 (8 eyes)</td>
</tr>
<tr>
<td>Glaucoma†</td>
<td>16 (16 eyes)</td>
</tr>
</tbody>
</table>

* Data are expressed as the mean ± SD.
† Six subjects with primary open-angle glaucoma, seven with normal-tension glaucoma, two with pigmentary glaucoma, and one with exfoliative glaucoma.
eyes (17%), the edge of BM constituted the disc margin with internally oblique border tissue of Elschnig.

Our results are generally consistent with a recent qualitative investigation on the cross-sectional configuration of PPA in normal subjects using FD-OCT, but describe the microstructural parapapillary anatomy in more detail using quantitative data. In the previous report, the authors mentioned that the photoreceptor IS/OS junction could be traced to the distal edge of the βPPA in all 120 subject eyes. We could also find gradual thinning of the IS/OS junction, but the IS/OS junction eventually ended slightly outside the βPPA with an intervening gap area of atrophied photoreceptor cells (mean horizontal width, 115 ± 59 μm). In addition, the edge of the RPE was identified, and it was elucidated that a short segment of RPE (mean, 17 ± 26 μm), the RPE-free BM of variable width (mean, 156 ± 120 μm), and the externally oblique border tissue of Elschnig (mean, 214 ± 204 μm) comprised the clinical βPPA beneath the retinal layers. Although atrophy implies an acquired loss of tissue, the border tissue of Elschnig represents congenital collagenous tissue arising from the sclera adjacent to the optic nerve exit from the eye. Therefore, we think that βPPA should be redefined to exclude the border tissue of Elschnig.

Another study of PPA using microperimetry reported that the psychophysical correlate of βPPA is an absolute scotoma and the correlate of the α-zone PPA is a relative scotoma. In our study, however, the IS/OS junction ended outside of the PPA in all 24 subject eyes, demonstrating that there is an irregular crescent-shaped zone peripheral and adjacent to the clinical βPPA where the photoreceptor cells may be atrophied or degenerated. Therefore, an absolute scotoma may be slightly more extensive than clinical βPPA, although the absence of visible IS/OS junction on FD-OCT does not necessarily imply loss of visual function.

The present study is partially limited, in that the βPPA only in the temporal 180° was analyzed with horizontal scans. Therefore, our results may not be applicable to the βPPA superior, nasal, or inferior to the optic disc. Also, our study investigated only the eyes with βPPA with a horizontal width of ≥150 μm in at least one meridian. Thus, the results may not apply to the eyes with smaller areas of βPPA. There may be minor disagreements between the disc margins in the color disc photograph and in the en face projection image, and those disagreements, if any, may have caused errors in the measurements, especially when the measured distances were very small (e.g., the distance between the temporal margin of βPPA and the edge of RPE). Careful interpretation is necessary for the distances measured in the present study (Table 2), because they are not actual distances between landmarks. In measuring the actual distance between structures, the effect of FD-OCT B-scan tilt should be corrected. We did not evaluate the α-zone PPA, not only because it is difficult to clearly delineate in the optic disc photograph, but also because it has little clinical significance. Although only patients with glaucoma or suspected glaucoma were examined in the present study, we do not think that our findings are exclusive to glaucomatous optic discs, as similar findings have been reported in normal human and monkey eyes.

It was difficult to demarcate the border of BM or the photoreceptor IS/OS junction ophtalmoscopically in eyes with conspicuous βPPA. Moreover, the RPE border was sometimes different from the ophtalmoscopically defined RPE border, which is the clinical βPPA border. Since these microstructures are important landmarks that can be used for optic nerve head and retinal nerve fiber layer analyses, sophisticated machines with advanced technology that can detect those microstructures should be able to provide additional information that may be useful in the diagnosis and management of glaucoma. We hypothesize that automated detection and quantification of βPPA would be helpful in glaucoma detection, risk stratification, and research.

References


