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Longitudinal Changes in Peripapillary Atrophy in the Ocular Hypertension Treatment Study

A Case–Control Assessment

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Purpose: To explore the association between peripapillary atrophy (PPA) area and conversion from ocular hypertension (OHT) to glaucoma.

Design: Prospective, longitudinal cohort study of cases and controls.

Participants: We included 279 age-matched and follow-up time–matched eyes with OHT that converted to glaucoma and 279 eyes with OHT that did not convert to glaucoma.

Methods: Initial and last acceptable optic disc photos were analyzed. Disc, α-zone, and β-zone PPA were traced independently by 2 trained readers and their areas were measured with Photoshop. The α-zone and β-zone areas were expressed as a percentage of optic disc area.

Main Outcome Measures: α-Zone and β-zone PPA size over time.

Results: Intraclass correlation coefficients (ICCs) demonstrated that readers had good agreement on disc area (ICC = 0.97) and β-zone (ICC = 0.82), but not α-zone (ICC = 0.48). The ß-zone, as a percentage of disc area, increased in size ($P < 0.001$) in both eyes with incident primary open-angle glaucoma (mean, 10.6%; standard deviation, 22.6%) and matched controls (mean, 10.1%; standard deviation, 33.7) over follow-up (mean, 12.3 years). The increase in size did not differ between cases and controls ($P = 0.82$). Enlargement of the β-zone was not correlated with follow-up time ($P = 0.39$).

Conclusions: The results did not show a difference in size of the β-zone at baseline between eyes that proceed to develop glaucoma and those that do not. Moreover, the β-zone enlarges equally in case and control eyes during follow-up. *Ophthalmology 2015;122:79-86 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Peripapillary atrophy (PPA) is among the parameters that are often taken into consideration in diagnosing open-angle glaucoma (OAG).[1,2] The association between PPA and OAG has been extensively investigated. Although there are a few studies to the contrary,[3–5] most cross-sectional[6–13] and prospective studies[14,15] have found that PPA is more frequent and larger in patients with OAG than those without OAG. Other longitudinal studies have demonstrated that PPA enlarges in some eyes as glaucoma progresses,[7,15–19] as well in some eyes with age.[15] It has also been reported that there is a significant association between the location of PPA and that of the most marked visual field loss[20–22] and that the extent of PPA significantly correlates with the degree of optic disc damage and visual field defects.[20,23,24]

There have been only a few reports on the prevalence of PPA in patients with ocular hypertension (OHT),[25,26] and the issue of whether the presence and/or progression of PPA is a risk factor for conversion from OHT to OAG remains uncertain.[5,27–31] However, many of these past investigations included relatively small numbers of patients, had poorly defined inclusion and exclusion criteria, and were cross-sectional rather than longitudinal. These limitations have also made it difficult to make comparisons across studies and highlight the need for more data to clarify the association between PPA progression in OHT and conversion to glaucoma. Because not all eyes with OHT develop OAG,[32–35] it is important to identify other factors, such as structural changes to the optic disc, that may help to determine the risk of conversion from OHT to glaucoma. Evaluation of a large set of prospectively collected data on PPA in OHT patients carries the potential to improve our understanding of the association of PPA and changes in PPA in OHT with conversion to glaucoma. The Ocular Hypertension Treatment Study (OHTS), which has provided

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the largest data set of prospectively collected information on patients with OHT, is well suited to studying the association of PPA progression in this group of subjects with the onset of glaucoma. The OHTS data files contain detailed demographic and clinical information, including evaluations of serial stereoscopic optic disc photographs taken annually and results of visual field testing performed every 6 months. The present study was designed to assess digitized photographs to explore whether PPA enlarges over time during the course of OHT and whether enlargement of PPA is associated with conversion to glaucoma.

Methods

Study Population

The patients enrolled in this study participated in the OHTS, whose protocol has been presented elsewhere.[35] The institutional review boards at all clinical sites approved their respective informed consent statements and procedures. The design of the OHTS followed the tenets of the Declaration of Helsinki.[36] The OHTS data set files include information of 3200 eyes from 1600 subjects studied from February 1994 to December 2009, with >300 eyes that converted from OHT to glaucoma through 2008 (Mae Gordon, personal communication, OHTS, January 2009). Determination of conversion to primary OAG (POAG) in the OHTS was defined as the development of a reproducible visual field abnormality and/or a reproducible optic disc change consistent with glaucoma in 1 or both eyes that was attributed to POAG by an end point committee masked to randomized treatment assignment. Definitions for visual field abnormality and optic disc deterioration are detailed elsewhere.[32]

This is a nested case−control study. Cases included 279 eyes of 279 participants with OHT that converted to POAG and controls were 279 eyes of 222 participants with OHT that did not meet conversion criteria in either eye. Case follow-up photographs were those collected at the last follow-up study visit. Control follow-up photographs were selected from eyes of participants who did not convert to glaucoma and matched with respect to eye laterality, participant age within 5 years, and study follow-up visit within 6 months. Controls and cases were matched by the same follow-up visit in all but 2 matches (1%) and by the same age (88% of matches), within 1 year of age (9% of matches), or within 2 to 5 years of age (3% of matches).

Optic Disc Slide Scanning and Digitization

Optic disc photographs in the OHTS were acquired at annual visits for both eyes after pupil dilation. All images were captured using 35-mm film-based technology. The images were then mounted in 2×2-inch slide format, labeled with individual anonymous codes to protect confidentiality, and stored at the Optic Disc Reading Center of the OHTS at the Bascom Palmer Eye Institute, University of Miami School of Medicine. Standard 35-mm Fujifilm 100 ASA (Fuji, Tokyo, Japan) was used for film capture because of its good image quality. Funding from the National Eye Institute supported the creation of a digital archive of all stereoscopic disc photographs collected during the OHTS. All original photographic transparencies of all subjects' visits were then digitized in RGB format using a Nikon Super CoolScan 5000ED scanner with SilverFast Ai software (LaserSoft Imaging Inc., Sarasota, FL) and saved in tagged image file format (.tiff). If the disc photos were taken with a sequential fundus camera, left and right images were scanned individually, cropped with Adobe Photoshop 3.0 (Adobe Systems, Inc., Mountain View, CA), placed side by side, and then saved as a single image of the stereoscopic pair. Disc photos taken with a simultaneous fundus camera were scanned and saved with no image manipulation. All images were labeled after the scanning process and moved to server storage.

Scanned Optic Disc Image Evaluation and PPA Margin Delineation

Baseline and study follow-up visit digital stereoscopic optic disc photographs of eyes with glaucoma and matched controls were retrieved from the server and presented on an interactive battery-free pen and liquid crystal display unit (Cintiq 12WX; Wacom, Vancouver, WA) for evaluation. Stereoscopic disc photographs with poor image quality (e.g., owing to cataract or technical reasons) that prevented reliably outlining the disc margin or the boundaries of the peripapillary zones α and β[37] were excluded and replaced by the one taken immediately after (if a baseline photograph) or immediately before (if a follow-up photograph). Each stereoscopic photograph was evaluated independently by 2 readers (E.S., R.V.) from the Optic Disc Reading Center of the OHTS using a handheld stereoscope (Screen-VU, Portland, OR) to view the images stereoscopically on the liquid crystal display. The Optic Disc Reading Center readers underwent extensive training in identification of optic disc structures and tracing by a senior investigator (D.R.A.).

The drawing tool (pen) was calibrated before each tracing session and standardized in terms of tip size (in pixels) and hardness. The structures to be quantified (optic disc, peripapillary zones α and β areas) were outlined on the inside edge so that the thickness of the trace would be incorporated in the total delineated area. Images were evaluated in a masked fashion without knowledge of the clinical diagnosis or other clinical information.

The border of the optic disc was defined as the inner margin of the peripapillary scleral ring of Elschnig, recognized as a white band seen in part of or all around the circumference of the optic disc, or by the boundary between disc tissue and retinal pigment epithelium when it obscured the scleral ring. The PPA was differentiated into the α-zone and β-zone as described by Jonas et al.[37] The α-zone was defined as an irregular area of hypopigmentation and hyperpigmentation adjacent to the scleral ring or located on the outer side of the β-zone if present. The β-zone, when present, extended from the scleral ring and was characterized by the absent retinal pigment epithelium, making visible the sclera or the choroid with its large vessels. The peripapillary scleral ring was included in the measurements of the β-zone (Fig 1). Because the width of the scleral ring was usually very thin, any error introduced by adding the scleral ring area to the β-zone was considered to be inconsequential. For each stereoscopic image, readers outlined successively 3 concentric regions: The edge of the optic disc, the area occupied by the optic disc and the PPA β-zone, and the region including optic disc and PPA β-zone and α-zone on the right side of the stereo pair, unless the left side provided a better quality image.

Planimetric Analysis

Measuring tools in Adobe Photoshop were used to generate the areas automatically, in pixels, on an outlined image. For each disc image, the software calculated the areas corresponding to disc area, along the inner edge of the scleral ring, if visible, a second area that included the optic disc with any visible scleral rim and the β-zone (if present), and a third area that included the previous plus the α-zone (if present).

The α-zone and β-zone areas (obtained by subtracting the 3 traced outlines) were normalized to the optic disc area by expressing it as a percentage of the disc area to minimize the effects