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Deep Retinal Layer Microvasculature Dropout Detected by the Optical Coherence Tomography Angiography in Glaucoma

Min Hee Suh, MD,[1,2] *Linda M. Zangwill, PhD,*[1] *Patricia Isabel C. Manalastas, MD,*[1] *Akram Belghith, PhD,*[1] *Adeleh Yarmohammadi, MD,*[1] *Felipe A. Medeiros, MD, PhD,*[1] *Alberto Diniz-Filho, MD, PhD,*[1] *Luke J. Saunders, PhD,*[1] *Robert N. Weinreb, MD*[1]

Purpose: To investigate factors associated with dropout of the parapapillary deep retinal layer microvasculature assessed by optical coherence tomography angiography (OCTA) in glaucomatous eyes.

Design: Cross-sectional study.

Participants: Seventy-one eyes from 71 primary open-angle glaucoma (POAG) patients with β-zone parapapillary atrophy (βPPA) enrolled in the Diagnostic Innovations in Glaucoma Study.

Methods: Parapapillary deep-layer microvasculature dropout was defined as a complete loss of the microvasculature located within the deep retinal layer of the βPPA from OCTA-derived optic nerve head vessel density maps by standardized qualitative assessment. Circumpapillary vessel density (cpVD) within the retinal nerve fiber layer (RNFL) also was calculated using OCTA. Choroidal thickness and presence of focal lamina cribrosa (LC) defects were determined using swept-source optical coherence tomography.

Main Outcome Measures: Presence of parapapillary deep-layer microvasculature dropout. Parameters including age, systolic and diastolic blood pressure, axial length, intraocular pressure, disc hemorrhage, cpVD, visual field (VF) mean deviation (MD), focal LC defects βPPA area, and choroidal thickness were analyzed.

Results: Parapapillary deep-layer microvasculature dropout was detected in 37 POAG eyes (52.1%). Eyes with microvasculature dropout had a higher prevalence of LC defects (70.3% vs. 32.4%), lower cpVD (52.7% vs. 58.8%), worse VF MD (−9.06 dB vs. −3.83 dB), thinner total choroidal thickness (126.5 μm vs. 169.1 μm), longer axial length (24.7 mm vs. 24.0 mm), larger βPPA (1.2 mm^2 vs. 0.76 mm^2), and lower diastolic blood pressure (74.7 mmHg vs. 81.7 mmHg) than those without dropout ($P < 0.05$, respectively). In the multivariate logistic regression analysis, higher prevalence of focal LC defects (odds ratio [OR], 6.27; $P = 0.012$), reduced cpVD (OR, 1.27; $P = 0.002$), worse VF MD (OR, 1.27; $P = 0.001$), thinner choroidal thickness (OR, 1.02; $P = 0.014$), and lower diastolic blood pressure (OR, 1.16; $P = 0.003$) were associated significantly with the dropout.

Conclusions: Systemic and ocular factors including focal LC defects more advanced glaucoma, reduced RNFL vessel density, thinner choroidal thickness, and lower diastolic blood pressure were factors associated with the parapapillary deep-layer microvasculature dropout in glaucomatous eyes. Longitudinal studies are required to elucidate the temporal relationship between parapapillary deep-layer microvasculature dropout and systemic and ocular factors. *Ophthalmology 2016;■:1−10 © 2016 by the American Academy of Ophthalmology*

A potential pathogenic role for the microvasculature and ocular blood flow in the development and progression of glaucomatous optic neuropathy has long been recognized.[1,2] The deep retinal layer microvasculature within the parapapillary area is of particular clinical interest because it is downstream from the short posterior ciliary artery,[3−7] which also perfuses the deep optic nerve head (ONH) structures.[5−7] Therefore, microvasculature within the β-zone parapapillary atrophy (βPPA) may be related to the vascular and mechanical properties of the deep structures such as prelaminar and laminar tissue. Moreover, there have been several reports that reduced choroidal vasculature may be related to the development of glaucoma.[3,8] However, in vivo visualization of the parapapillary deep-layer microvasculature has been problematic. Previous investigations had to rely on invasive imaging methods such as fluorescein angiography or indocyanine green angiography that could not distinguish this layer.[3,4]

With the recent development of optical coherence tomography angiography (OCTA), noninvasive in vivo imaging of the microvasculature located within various retinal layers is possible.[9−12] There are a limited number of studies documenting the sparser microvasculature in the retinal nerve fiber layer (RNFL) in eyes of glaucoma patients compared with glaucoma suspects and healthy participants.[12] However, little is known about the visualization of the deep-layer microvasculature within the βPPA area.

The purpose of this study was to characterize dropout of the deep retinal layer microvasculature within the βPPA in

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primary open-angle glaucoma (POAG) patients. In addition, the relationship between the dropout and clinical characteristics such as glaucoma severity, focal lamina cribrosa (LC) defects, and choroidal thickness was investigated.

Methods

Primary open-angle glaucoma patients from the Diagnostic Innovations in Glaucoma Study (ClinicalTrials.gov identifier, NCT00221897) were included. Details of the Diagnostic Innovations in Glaucoma Study protocol and eligibility have been described previously.[13] This study was approved by the Institutional Review Board at the University of California, San Diego, and conformed to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Informed consent was obtained from all participants.

Participants

Established POAG patients with confirmed βPPA derived from standardized photographic assessment who completed OCTA imaging and ONH imaging using both spectral-domain (SD) optical coherence tomography (OCT) and swept-source (SS) OCT were enrolled. All participants underwent an ophthalmologic examination, including assessment of best-corrected visual acuity, refractive error, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, central corneal thickness (CCT) measured with ultrasound pachymetry (DGH Technology, Inc, Exton, PA), axial length measured by the IOL Master (Carl Zeiss Meditec, Dublin, CA), dilated fundus examination, simultaneous stereophotography of the optic disc, standard automated perimetry (Humphrey Field Analyzer; 24-2 Swedish interactive threshold algorithm; Carl-Zeiss Meditec), SD OCT, OCTA, and SS OCT. Perimetry and all imaging tests were conducted within a 6-month period.

Systolic and diastolic blood pressure (BP) and pulse rate were measured twice with an Omron Automatic (Model BP791IT; Omron Healthcare, Inc., Lake Forest, IL) BP instrument, and the mean values were used in the analysis. Mean arterial pressure was derived as: 1/3 systolic BP + 2/3 diastolic BP. Mean ocular perfusion pressure was calculated as the difference between two thirds of mean arterial pressure and IOP.

Presence of optic disc hemorrhage and βPPA was determined based on optic disc stereophotographs obtained at the participants' annual dilated examination. Glaucomatous optic disc hemorrhage was defined as an isolated splinter or flame-shaped hemorrhage on optic disc tissue or crossing the optic disc.[14] β-zone parapapillary atrophy was defined as an atrophy of the retinal pigment epithelium and visibility of the large choroidal vessels and the sclera.[15,16] Two independent observers masked to patient information and test results independently evaluated each image. Discrepancies between the 2 observers (M.H.S., P.C.M) were resolved by consensus.

To be included, participants were required to have been diagnosed with POAG, to be older than 18 years, to have best-corrected visual acuity of 20/40 or better, and to have an open angle by gonioscopy. Participants with a history of ocular intervention (except for uncomplicated cataract or glaucoma surgery), intraocular diseases (e.g., diabetic retinopathy or nonglaucomatous optic neuropathy), or systemic diseases (e.g., stroke or pituitary tumor) that could influence the study results were excluded. Those with systemic hypertension and diabetes mellitus were included unless they were diagnosed with diabetic or hypertensive retinopathy. Participants with unreliable visual fields (VFs) or poor-quality imaging test results also were excluded.

Primary open-angle glaucoma was defined as the presence of glaucomatous optic nerve damage (i.e., the presence of focal thinning, notching, or localized or diffuse atrophy of the RNFL) based on standardized assessment of simultaneous stereophotographs and associated repeatable VF damage. Glaucomatous VF damage was defined as VF results outside normal limits on the glaucoma hemifield test or pattern standard deviation outside 95% of normal limits confirmed on 2 consecutive, reliable (fixation losses and false-negative rates $\leq$33% and false-positive rate $\leq$15%) tests.

Spectral-Domain Optical Coherence Tomography Imaging

All participants underwent ONH imaging with a commercially available SD OCT system (Avanti; Optovue, Inc, Fremont, CA) using a light source with a 70-kHz axial line rate and with a center wavelength of 840 nm. The ONH map protocol calculates disc area and circumpapillary RNFL (cpRNFL) thicknesses in a 10-pixel−wide band along a circle of 3.45 mm in diameter centered on the ONH based on 360° global area. Only good-quality images with a signal strength index of 37 or more and without segmentation failure or artifacts were included.[12]

Optical Coherence Tomography Angiography Imaging

The Angiovue (Optovue, Inc) incorporated in the Avanti SD OCT system provides a noninvasive visualization of the vascular structures of various user-defined retinal layers by using the motion contrast technique and split-spectrum amplitude-decorrelation angiography method. Details have been described elsewhere.[9,12,17−19] Briefly, the OCTA image is based on an amplitude decorrelation between 2 rapidly repeated B-scans, and the SD OCT image consists of the average of the 2 rapid repeats at the same B-scan location. In addition, the split-spectrum amplitude-decorrelation angiography technique allows high-resolution 3-dimensional visualization of perfused retinal microvasculature. Image quality review was performed on all whole depth images according to a standard protocol established by the Imaging Data Evaluation and Analysis reading center. Trained observers (M.H.S., P.C.M., and A.Y.) reviewed scans and those with poor image quality, as defined by the following criteria, were excluded: (1) a signal strength index less than 48 (1 = minimum, 100 = maximum), (2) poor clarity, (3) residual motion artifacts visible as irregular vessel pattern or disc boundary on the en face angiogram, (4) local weak signal, and (5) segmentation errors of the RNFL and choroidal layer.[12] Scanning laser ophthalmoscopy (SLO) images of the Avanti SD OCT centered on the optic disc acquired at the same positions as the OCTA also were reviewed for the delineation of the disc margin and βPPA, as described below. Eyes with poor-quality SLO images in which the βPPA or optic disc were not clearly delineated also were excluded.

Vessel density (percent) of the microvasculature located in the RNFL layer was calculated as the proportion of measured area occupied by flowing or perfused blood vessels on the ONH images with a 4.5×4.5-mm field of view centered on the optic disc.[12] Two vessel density summary parameters in the RNFL were obtained: (1) whole image vessel density (wiVD) measured in the entire 4.5×4.5-mm image and (2) circumpapillary vessel density (cpVD) calculated in a region defined as a 750-μm-wide elliptical annulus extending from the optic disc boundary based on a 360° global area.[12,20]