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Central Visual Field Damage and Parapapillary Choroidal Microvasculature Dropout in Primary Open-Angle Glaucoma

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Purpose: To determine whether microvasculature dropout (MvD) in the parapapillary choroid is related to the presence of central visual field defects in primary open-angle glaucoma (POAG).

Design: Cross-sectional observational study.

Participants: Thirty-two POAG patients with an initial parafoveal scotoma (IPFS) within a 10° radius in 1 hemifield and 42 POAG patients with an initial nasal step (INS) within the nasal periphery outside 10° of fixation in 1 hemifield.

Methods: The peripapillary choroidal microvasculature was evaluated on en face images obtained using swept-source OCT angiography. Microvasculature dropout was defined as a focal sectoral capillary dropout with no visible microvascular network identified in the choroidal layer. Factors associated with IPFS, compared with INS, were assessed using logistic regression analyses.

Main Outcome Measures: Factors associated with IPFS rather than INS.

Results: Microvasculature dropout was observed in 25 of 32 eyes (78.1%) in the IPFS group, but in only 1 of 42 eyes (2.4%) in the INS group ($P < 0.001$). In logistic regression analyses, only MvD was a significant factor influencing the presence of IPFS. Systemic risk factors such as cold extremities ($P = 0.026$), migraine ($P = 0.044$), lower mean arterial pressure ($P = 0.037$), and lower ocular perfusion pressure ($P = 0.024$) were associated significantly with the presence of MvD.

Conclusions: The presence of MvD in the parapapillary choroid was a strong predictor for IPFS. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

Visual field (VF) defects near fixation are of particular concern in glaucoma because they can affect patient quality of life more significantly than peripheral VF defects.[1–3] The concern is even more serious when they appear early in the disease process. Parafoveal scotoma (PFS) has been reported to be associated with low intraocular pressure (IOP), suggesting that it is associated potentially with risk factors other than, or in addition to, elevated IOP.[4,5] More recent studies have shown that PFS is seen more frequently in patients with systemic vascular risk factors, such as systemic hypotension, migraine, and Raynaud's phenomenon,[6] and in eyes with narrower retinal vessels.[7] These findings suggest that specific patterns of glaucomatous VF loss may be associated with the underlying pathogenesis of glaucomatous optic neuropathy. However, the precise relationship between vascular mechanisms of optic nerve damage not related to IOP and the preferential occurrence of PFS remains to be determined.

Peripapillary choroidal microvasculature is of particular interest in glaucoma because it is supplied by the short posterior ciliary arteries, which also perfuse deep optic nerve head tissues. Recent studies using OCT angiography (OCTA) have identified localized microvasculature dropout (MvD) in the peripapillary choroid of glaucoma patients.[8,9] We showed that MvD detected by OCTA corresponds to the perfusion defect as assessed using indocyanine green angiography.[10] Suh et al[9] reported that the presence of MvD was related to a lower diastolic blood pressure (BP), which is suggested to be a potential vascular risk factor for glaucomatous optic neuropathy.[11–13]

Considering that both PFS and MvD have been associated with vascular risk factors, we hypothesized that there may be a close relationship between them. Thus, the purpose of this study was to determine whether MvD is associated with the appearance of PFS in the early phase of the disease. For the purposes of the study, glaucomatous eyes with early initial PFS (IPFS) and those with early initial nasal step (INS) were compared.

Methods

This study investigated the peripapillary circulation using OCTA in consecutive primary open-angle glaucoma (POAG) patients who were enrolled in the Investigating Glaucoma Progression Study, an ongoing prospective study of glaucoma patients at the Glaucoma Clinic of Seoul National University Bundang Hospital. Written informed consent to participate was obtained from all of the participants. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital and followed the tenets of the Declaration of Helsinki.

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All participants underwent comprehensive ophthalmic examinations that included best-corrected visual acuity, Goldmann applanation tonometry, a refraction test, slit-lamp biomicroscopy, gonioscopy, stereo disc photography, red-free fundus photography (EOS D60 digital camera; Canon, Utsunomiya, Japan), central corneal thickness measurement (Orbscan II; Bausch & Lomb Surgical, Rochester, NY), axial length measurement (IOLMaster version 5; Carl Zeiss Meditec, Dublin, CA), spectral-domain OCT scanning of the circumpapillary retinal nerve fiber layer (RNFL) and optic nerve head using enhanced depth imaging (Spectralis; Heidelberg Engineering), standard automated perimetry (Humphrey Field Analyzer II 750, 24-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec), and OCTA (DRI OCT Triton; Topcon, Tokyo, Japan). A clinical history also was obtained from the participants using a questionnaire, including demographic characteristics and the presence of cold extremities, migraine, and other systemic diseases. Systolic and diastolic BPs were measured at the time of OCTA. The mean arterial pressure (MAP) and ocular perfusion pressure (OPP) were calculated based on the following equations: MAP = diastolic BP + 1/3 (systolic BP − diastolic BP); OPP = 2/3 MAP − IOP at the time of OCTA.

Primary open-angle glaucoma was defined as the presence of an open iridocorneal angle, signs of glaucomatous optic nerve damage (i.e., neuroretinal rim thinning, notching, or an RNFL defect), and a glaucomatous VF defect. A glaucomatous VF defect was defined as a defect meeting 1 or more of the following criteria: results outside normal limits on a glaucoma hemifield test; 3 abnormal points with a $P < 0.05$ of being normal and 1 abnormal point with $P < 0.01$ by pattern deviation; or a pattern standard deviation of $P < 0.05$, confirmed on 2 consecutive reliable tests (fixation loss rate, ≤20%; false-positive and false-negative error rates, ≤25%). From the POAG patients, those with only an isolated IPFS or INS in 1 hemifield as defined below were enrolled. If both eyes of a patient were eligible, the eye with the worse VF mean deviation value was enrolled.

Eyes were required to have a record of untreated IOP that was measured before the initiation of ocular hypotensive treatment or was identified in the referral notes. In patients with an untreated IOP of 21 mmHg or less, the diurnal variation was measured during office hours (every 2 hours from 9 AM to 5 PM), and the mean of the 5 values was considered an untreated IOP. In those with an untreated IOP more than 21 mmHg, IOP was measured twice before starting IOP-lowering medication, and the mean of the 2 values was considered the untreated IOP. In patients who were undergoing treatment with ocular hypotensive medication at the time of the initial visit, the diurnal variation was measured after a 4-week washout period. The exclusion criteria were eyes with a best-corrected visual acuity worse than 20/40; a spherical equivalent less than 9.0 diopters (D) or more than +3.0 D; a cylinder correction less than 3.0 D or more than +3.0 D; a history of intraocular surgery, with the exception of uneventful cataract surgery or trabeculectomy; and retinal or neurologic diseases. Eyes with optic disc tilt (ratio of the longest diameter to the shortest diameter of the optic disc, >1.3)[14] also were excluded. This was because such eyes may have PFS because of a nonvascular mechanism.[15,16]

Definitions of Visual Field Defects

Initial PFS and INS were defined based on the criteria described elsewhere.[6,17] An IPFS was defined as a glaucomatous VF defect in 1 hemifield within 12 points of a central 10° of fixation, and no VF abnormality in the nasal periphery outside 10° of fixation (Fig 1). An INS was defined as a glaucomatous VF defect in 1 hemifield in the nasal periphery outside 10° of fixation, and no abnormalities within the central 10° (Fig 1). Criteria for an IPFS or INS VF defect were the presence of 3 or more points with $P < 0.05$, one of which had $P < 0.01$, among 12 points in each group on the pattern deviation plot.

OCT Angiography

The optic nerve and peripapillary area were imaged using a commercially available swept-source OCTA device (DRI OCT Triton), with a central wavelength of 1050 nm, an acquisition speed of 100 000 A scans per second, and an axial and transversal resolution of 7 and 20 μm in tissue, respectively. Scans were obtained from 4.5 × 4.5-mm cubes, with each cube consisting of 320 clusters of 4 repeated B scans centered on the optic disc. En face projections of volumetric scans allowed visualization of structural and vascular details within segmented retinal or choroidal layers.

The choroidal microvasculature in the peripapillary area was evaluated in en face images of the peripapillary deep layer, generated based on the automated layer segmentation performed by the OCT instrument software. The en face images of the deep layer were derived from an en face slab, extending from the retinal pigment epithelium to 390 μm below Bruch's membrane, which was sufficient to include the full thickness of the choroid and the inner scleral surface (Fig 2A).

Microvasculature dropout was defined as a focal sectoral capillary dropout with no visible microvascular network identified

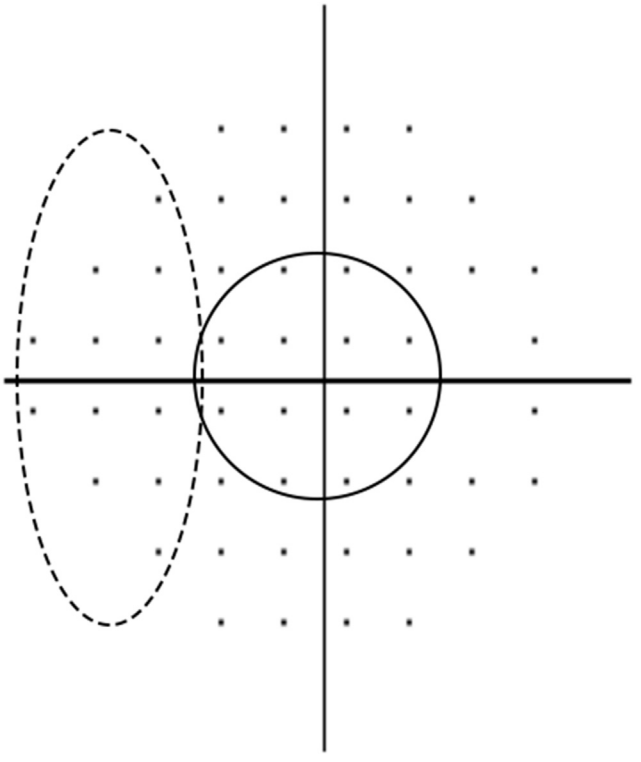

Figure 1. Pattern deviation plot, divided into 2 subfields of the Humphrey visual field. The initial parafoveal scotoma group includes abnormal points within 12 points of a central 10° of fixation (*solid circle*) in 1 hemifield and no abnormalities within the 12 nasal peripheral points (*dashed circle*). The initial nasal step group has abnormal points within 12 nasal peripheral points (*dashed circle*) in 1 hemifield and no abnormalities within the central 10° (*solid circle*). Both groups could have abnormal points outside the demarcated lines, as long as they did not interrupt the field of each other. However, these abnormal points outside the borders should occur to a lesser degree compared with the parafoveal or nasal scotoma.