Comparison of Peripapillary Choroidal Microvasculature Dropout in Primary Open-angle, Primary Angle-closure, and Pseudoexfoliation Glaucoma

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Precis: The prevalence of choroidal microvascular dropout (CMvD) was significantly higher in primary open-angle glaucoma (POAG) than primary angle-closure glaucoma (PACG) or pseudoexfoliation glaucoma (PXG) in the early stage. However, in the advanced stage, it did not differ among the 3 groups.

Purpose: The purpose of this study was to compare the prevalence of peripapillary CMvD in POAG, PACG, and PXG.

Materials and Methods: The presence of peripapillary CMvD was identified using optical coherence tomography angiography (AngioVue/RTVue-XR) imaging of the choroid in 186 eyes from 186 subjects [age and visual field (VF) mean deviation (MD) matched; 62 POAG, 62 PACG, and 62 PXG eyes]. Prevalence of CMvD was compared among glaucoma types in early and moderate to advanced disease, as divided by VF MD (~6 dB). The association between glaucoma type and presence of CMvD was evaluated using logistic regression analysis.

Results: Prevalence of CMvD was significantly different between glaucoma types in early-stage disease (PACG 7.5%, PXG 25%, and POAG 46.3%, P < 0.001), but it did not differ between glaucoma types in eyes with moderate to advanced disease (PACG 59.1%, PXG 68.2%, and POAG 81%; P = 0.331). After adjusting for age, sex, the β-zone peripapillary atrophy/disc ratio, and glaucoma severity (VF MD), the CMvD odds ratio was 7.50 times greater in POAG than in PACG (P = 0.001).

Conclusions: CMvD was more common in POAG relative to both PACG and PXG, especially in early-stage disease. This finding suggested a role for ischemic injury in the pathogenesis of POAG.

Key Words: primary open-angle glaucoma, primary angle-closure glaucoma, pseudoexfoliation glaucoma, choroidal microvascular dropout

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Original Study

A recently developed live imaging technique, optical coherence tomography angiography (OCT-A), allows evaluation of the parapapillary and macular microvasculature. These measurements are used as indicators to assess glaucoma severity, together with structural measures such as retinal nerve fiber layer (RNFL) or ganglion cell complex thickness, and functional tools such as visual field (VF).

Further, exploration of the peripapillary and macular microvasculature will yield insight into the pathogenesis of glaucoma. Peripapillary choroidal microvascular dropout (CMvD) within the β-zone peripapillary atrophy (β-PPA) adjacent to the optic nerve head (ONH) was observed in primary open-angle glaucoma (POAG) eyes, and numerous studies have assessed the clinical implication of this finding. CMvD is associated with disc hemorrhage, focal lamina cribrosa defect, and central VF loss. Furthermore, recent studies demonstrated a higher rate of RNFL loss and VF progression in glaucomatous eyes with CMvD. Hence, the clinical implications of CMvD are potentially important, but its etiology remains incompletely understood.

Comparing the prevalence of CMvD among different types of glaucoma can yield insights into its clinical significance and etiology, as glaucomatous pathology may differ between types of glaucoma. Hence, in the present study, we investigated the prevalence and factors associated with CMvD in the 3 most common types of glaucoma: primary angle-closure glaucoma (PACG), pseudoexfoliation glaucoma (PXG), and POAG.

Materials and Methods

Study Participants

The medical records of glaucoma patients who visited and were examined at the glaucoma clinic of the Asan Medical Center, Seoul, Korea, from January 2017, to July 2019, were reviewed, and subjects who met the below inclusion criteria were consecutively enrolled. The retrospective study protocol was approved by the Ethics committee/Institutional Review Board of the Asan Medical Center (ID: 2017-1311) and conformed to the principles of the Declaration of Helsinki. As this study was a retrospective study, the requirement for informed consent was waived.

All subjects underwent a comprehensive ocular examination, including a review of past medical history, slit-lamp biomicroscopy, measurement of best-corrected visual acuity with refraction, Goldmann applanation tonometry, and gonioscopy. Patients also underwent dilated color fundus photography (Canon, Tokyo, Japan), ONH stereoscopic photography, red-free RNFL photography, and (Canon), Humphrey field analyser Swedish Interactive Threshold Algorithm 24-2 VF testing (Carl Zeiss Meditec, Dublin, CA). Central corneal thickness was determined using ultrasound.
pachymetry (DGH-550; DGH Technology Inc., Exton, PA) and axial length by IOL Master (Carl Zeiss Meditec).

Glaucoma was diagnosed as the presence of typical glaucomatous ONH damage, such as neuroretinal rim thinning, notching, and RNFL defects. In addition, the presence of compatible glaucomatous VF defects was assessed following Anderson’s criteria and confirmed on 2 consecutive reliable VF tests. A reliable VF assessment was defined as a VF test with false-positive and false-negative errors <15%, and a fixation loss <20%. POAG was defined as the presence of an open iridocorneal angle on the gonioscopic examination, and PXG was defined as the presence of pseudoexfoliation material visible on the iris margin or the anterior capsule of the lens. PACG was defined as the presence of a closed angle, invisibility of the pigmented trabecular meshwork for at least 180 degrees on gonioscopy in the primary position without indentation. PACG exhibited features indicating trabecular meshwork closure by the peripheral iris, including elevated intraocular pressure (IOP), peripheral anterior synechiae, glaukomfleck on the lens, iris whirling, or excessive pigment deposition on the angle.

Inclusion criteria were as follows: (1) age older than 18 years; (2) best-corrected visual acuity ≥20/40 with a spherical equivalent within ±6 D; (3) reliable OCT-A images (signal strength index ≥45, no projection or motion artefact and no segmentation error); and (4) a visible β-PPA on fundus photography. Eyes with a history of the following were excluded: (1) ophthalmic or neurological disease that could affect the VF test or ONH examination; or (2) intraocular surgery, except for uncomplicated cataract surgery. If both eyes in a single subject were eligible for the study, one eye was randomly selected for analysis. The eyes were divided according to glaucoma severity (VF MD = −6 D) for subgroup analysis.

OCT-A

All patients underwent OCT-A scanning with an AngioVue (Optovue Inc., Fremont, CA). This process scans the optic disc using an 840 nm diode laser source, and a split spectrum amplitude-decorrelation angiography algorithm is used to detect the dynamic flow of red blood cells. This allows for noninvasive, 3-dimensional microvascular imaging on the capillary level. The built-in software of AngioVue provides circumpapillary vessel density (cpVD) automatically at various user-defined retinal layers, both qualitatively and quantitatively (version 2017.1). Poor-quality OCT-A images with a signal strength index <45 or blurred images that obscured delineation of the disc margins, peripapillary atrophy (PPA), or CMvD were excluded from the analysis. Retinal nerve fiber layer thickness (RNFLT) was also measured in all patients using an OCT-A ONH scan of a 3.4 mm circle around the disc center.

β-PPA and CMvD Assessment

β-PPA was defined as the presence of an inner crescent chorioretinal atrophy area with the visible sclera and choroidal vessels adjacent to the optic disc based on color fundus photography images. The clinical disc and β-PPA margins were manually delineated based on color fundus photography, and their areas were measured using ImageJ software (version 1.51; Wayne Rasband, National Institutes of Health, Bethesda, MD). The β-PPA/disc ratio was calculated to minimize the magnification error of the photography and to accurately represent the dimensions of the β-PPA (Fig. 1A). Two glaucoma specialists (Y.H.J. and J.W.S.) measured the areas in blinded images, and the average of the values obtained by the 2 investigators was used for analysis to minimize interexaminer variation.

The presence of CMvD within the β-PPA was defined as a complete focal loss of the choriocapillaris with a minimum angular width >200 μm based on OCT-A choroidal slab images, as defined in previous studies (Fig. 1B). Evaluation of CMvD was also conducted by 2 glaucoma specialists (Y.H.J. and J.W.S.) in masked images, and any disagreements between observers were resolved by a third adjudicator (K.R.S.).

Statistical Analysis

Interexaminer agreement for the size of the β-PPA and disc, and the presence of CMvD, was assessed by intraclass correlation coefficients and κ statistics. Normal data distribution

FIGURE 1. Evaluation of choroidal microvascular dropout in eyes with glaucoma. A, The β-zone peripapillary atrophy (yellow dotted outline) and optic disc margin (blue dotted outline) were manually demarcated on color fundus photography. B, Choroidal microvascular dropout (red solid line) was marked on the choroidal slab. Figure 1 can be viewed in color online at www.glaucomajournal.com.
was confirmed using the Kolmogorov-Smirnov test. The comparison was performed with continuous variables using a 1-way analysis of variance with Dunnett T3 or Bonferroni post hoc tests among 3 groups. β-PPA/disc, cpVD, and RNFLT were compared after adjusting for VF MD by analysis of covariance because the differences of VF MD was marginally significant among 3 groups in early stage ($P = 0.096$). For categorical variables, a $\chi^2$ test was used. The association between CMvD and glaucoma type was determined by univariate and multivariate logistic regression analyses. Univariate analyses were performed with each variable, including demographics, structural and vascular measurements, and glaucoma type, and variables with $P$-value <0.1 were included in multivariate regression analysis using a backward elimination approach. Factors associated with CMvD were also explored in each glaucoma group. All statistical analyses were performed with SPSS software, version 18.0 for Windows (SPSS Inc., Chicago, IL), and $P$-values <0.05 were considered statistically significant.

**RESULTS**

One hundred ninety-nine patients who met the initial inclusion criteria were evaluated. Of them, 13 eyes (6.5%) were excluded because of the poor image quality of OCT-A for CMvD evaluation. Therefore, a total of 186 eyes (age and VF MD matched; 62 POAG, 62 PXG, and 62 PACG) were included in the final analysis. Interexaminer agreement for the detection of CMvD was excellent ($κ = 0.925$), and intraclass correlation coefficients for measurements of β-PPA and optic disc areas using color fundus photography were 0.905 and 0.946, respectively.

IOP was marginally higher in PXG compared with POAG, and axial length was significantly shorter in PACG compared with both POAG and PXG. However, other factors, including VF MD, RNFLT, cpVD, and the β-PPA/disc ratio did not differ between groups. Overall, the prevalence of CMvD was significantly higher in POAG (58.1%) compared with both PACG (25.8%, $P < 0.001$) and PXG (40.3%, $P = 0.048$). In a comparison of PACG and PXG, it was marginally higher in PXG than in PACG, although this trend did not reach statistical significance ($P = 0.063$, Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A446).

When we divided all subjects into 2 groups according to glaucoma severity (early and moderate to advanced; cutoff VF MD = −6D), all 3 groups had a greater prevalence of CMvD in the moderate to advanced group compared with the early group. In early-stage disease, the prevalence of CMvD was significantly different among groups ($P < 0.001$). It was lowest in PACG (7.5%), followed by PXG (25%) and POAG (46.3%), and significantly different between PACG and POAG ($P < 0.001$), and marginally different between PACG and PXG ($P = 0.066$), and between PXG and POAG ($P = 0.064$) in the early group. However, it was not statistically different among the 3 groups in moderate to advanced-stage disease ($P = 0.331$, Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/IJG/A446).

In univariate logistic regression analysis, the odds ratio for the presence of CMvD was 1.94 times greater in PXG and 3.98 times greater in POAG compared with the PACG group. As VF MD, RNFLT, and cpVD were significantly correlated with each other ($P < 0.001$, respectively), these variables included separately in the multivariate models to avoid multicollinearity. In multivariate model 1, after adjusting for age, sex, β-PPA/disc ratio, and VF MD, the odds ratio for CMvD was 2.28 times greater in PXG and 7.50 times greater in POAG than in PACG ($P = 0.001$). The multivariate models 2 and 3 which adjusted for age, sex, β-PPA/disc ratio, and RNFLT (model 2), and cpVD (model 3), respectively, showed similar results (Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/IJG/A446).

We subsequently evaluated the factors associated with the presence of CMvD in each glaucoma group. The factors associated with CMvD prevalence were slightly different in univariate analysis, but the severity of glaucoma (VF MD, RNFLT, and cpVD) was significantly associated with CMvD in multivariate analyses of all 3 groups (Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/IJG/A446).

Representative cases are shown in Figure 2. In the early-stage group (Fig. 2A), a 66-year-old man with POAG (MD = −1.61D) exhibited CMvD in the inferotemporal area, but a 62-year-old woman with PACG (MD = −1.83D) and PXG (MD = −1.58) had no CMvD. In the moderate to severe group (Fig. 2B), a 68-year-old man with POAG (MD = −18.56), a 66-year-old woman with PACG (MD = −18.39) and a 62-year-old woman with PXG all exhibited large areas of CMvD.

**DISCUSSION**

After CMvD was confirmed to be a true blood flow defect by indocyanine green angiography, many studies explored the clinical implications of CMvD in glaucoma pathogenesis.4,5 No currently available studies have established whether CMvD is a primary event of glaucoma pathology or a secondary result of progressing glaucomatous damage. We, therefore, sought to gain insight into the etiology and clinical significance of CMvD by evaluating its prevalence in different types and severities of glaucoma.

The overall prevalence of CMvD was greatest in POAG (58.1%), followed by PXG (40.3%) and PACG (25.8%). This result was consistent with the subgroups analysis of early stage; POAG (46.3%), PXG (25%), and PACG (7.5%). The prevalence of CMvD in PACG was significantly lower than that in POAG, which was consistent with a previous study by Rao et al.19 This could be explained by differential mechanisms of damage to the retinal ganglion cells between the 2 types of glaucoma. PACG develops due to increased IOP secondary to mechanical obstruction of aqueous outflow. Contrastingly, other vascular dysfunctions and ischemic events may contribute to the pathogenesis of POAG in addition to the mechanical effect, especially in normal-tension POAG.14,20 In this study, although there was no difference in IOP between 2 groups at initial evaluation because it might be controlled by glaucoma medications or laser peripheral iridotomy, 27 eyes (43.5%) of PACG eyes had a history of acute angle-closure attack. Further, PACG is known to have intermittent IOP spikes which may not be detected during a clinic visit.21 In contrast, 49 of 62 POAG patients (80%) were classified as normal-tension glaucoma (NTG), which can be considered to re ect the distribution of Korean open-angle glaucoma patients as reported in population-based NAMIL study.22 A prior study reported that in POAG eyes, especially NTG, CMvD was associated with a reduction of ocular perfusion pressure and increase of parafoveal scotoma, implying the role of ischemic injury in glaucomatous damage.5,23 In addition, a recent study revealed that the CMvD is associated with an impaired choroidal vascular function within the β-PPA.24 The short posterior ciliary arteries supply both the parapapillary choroid and the deep ONH tissue.
with intricately interconnected branches. Therefore, focal occlusion of vessels that promotes CMvD could suggest vascular insufficiency in the ONH. These findings suggest that the presence of CMvD represents perfusion defects around the ONH and that CMvD could be a marker to explain the ischemic mechanism of POAG development and progression. Therefore, a higher prevalence of CMvD in POAG can be explained as a result of reflecting the ischemic mechanism in glaucoma development.

CMvD was also significantly less prevalent in PXG than in POAG, which is consistent with a prior study. Although the statistical significance of this relationship was weakened after dividing all glaucoma types into early and moderate to advanced groups, the prevalence of CMvD was still higher in POAG (46.3%) than in PXG (25%). Because IOP is generally higher in PXG and PACG than in POAG, CMvD could develop via a different mechanism as mentioned earlier. In other words, we speculated that the presence of CMvD could represent ischemic damage, and thus it is less frequent in glaucomatous eyes with relatively higher IOP like PXG. Hence, this outcome also suggested that the greater prevalence of CMvD in POAG than in PXG could be due to glaucomatous ischemic injury in POAG.

There were conflicting results in comparison of cpVD between PXG and POAG, which may be due to different study designs or measurement devices or study subjects. Our group recently reported that age and glaucoma severity matched PXG and POAG eyes didn’t significantly differ in superficial and deep vessel density (VD) in both early and advanced stages. Suwan et al reported that average peripapillary VD and VDs in all sectors were lower in PXG than in POAG, but the authors did not match the subjects’ age or glaucoma severity between groups, so PXG group had significantly older subjects than POAG. Further, they used custom software to measure and compare VDs, which may also have affected the outcome. Park et al found that cpVD was decreased in PXG for only the average, nasal, and inferonasal sectors. However, the differences were only marginally significant. They used a swept-source optical coherence tomography device, which is different from that used in our study, and obtained VD data using custom software after removing the major vessels using Photoshop software (Adobe, San Jose, CA).

In our present study, we compared the cpVD and RNFLT after age and glaucoma severity matching and there were no significant differences in both cpVD and RNFLT between 2 groups. This result was in line with that of previous studies. Hence, the result may be explained that reduction of cpVD is a secondary change at the area of glaucomatous RNFLT atrophy but this should be investigated in the forthcoming longitudinal study.

Interestingly, there was no difference in the prevalence of CMvD among 3 different glaucoma types in moderate to severe group.
an advanced stage. This suggested that although the prevalence of CMvD was significantly different between glaucoma types in early-stage disease, CMvD increased in all types of glaucoma with disease progression, and its prevalence did not differ between glaucoma types in subjects with advanced disease. This finding is not explained by prior speculation that CMvD could represent ischemic damage. According to a prior study, the prevalence of CMvD not only increases with glaucoma progression, but CMvD prevalence exhibits topographical correspondence with RNFL defects. Therefore, this outcome suggested the possibility that CMvD may develop or progress secondary to glaucomatous RNFL thinning. CMvD could be caused by the regression of supplying vessels due to the reduced metabolic demand of damaged axons. In addition, our findings demonstrated that the prevalence of CMvD was associated with the severity of glaucoma in all 3 types of glaucoma, which was consistent with the outcome of previous studies. Another possible interpretation is that CMvD primarily contributes more to the glaucomatous damage in severe cases of PXG and PACG than it does in mild cases. However, further longitudinal studies are required to better understand the role of CMvD in the pathogenesis of PXG and PACG.

In subgroup analyses, CMvD was associated with functional (VF MD) and structural glaucomatous (RNFL and cpVD) damage in all 3 glaucoma groups. Therefore, CMvD could be used as a biomarker which can evaluate glaucomatous damage and progression regardless of the glaucoma type. Rao et al. reported that CMvD in PACG was associated only with VF MD but not with RNFL and cpVD. The discrepancy with our result may arise from the relatively smaller number of their PACG subjects (28 eyes) than ours (62 eyes).

Although these findings do not establish a cause and effect relationship between CMvD and glaucoma, but suggest that CMvD can occur either as a primary event of disease or secondary to glaucomatous damage with the progression of disease in the context of glaucoma. This speculation should be confirmed in a longitudinal study to determine the temporal relationship between glaucomatous damage and the development of CMvD.

There are a few limitations in the present study that should be acknowledged to avoid over the interpretation of the outcome. First, the study is subject to selection bias, as the subjects were enrolled in a retrospective manner at a referral tertiary care service. To address this bias, studies of the general population will be needed in the future. Second, visualization of the deep choroidal microvasculature can be prohibitive in OCT-A. Projection artefacts and signals from the superficial retinal vessels can affect the detection of CMvD. Third, systemic blood pressure and pulse rate data are missing in the present study. A prior study reported that in POAG, low diastolic blood pressure was associated with the presence of CMvD, and pulse rate was also reported to be related with choroidal image intensity on the PPA zone in NTG with the myopic disc. Further studies regarding the relationship between systemic blood pressure, as well as pulse rate, and CMvD prevalence should be conducted not only in POAG but also in PACG and PXG. Fourth, the use of systemic hypertensive medication or IOP-lowering agents may affect CMvD. Previous studies reported topical glaucoma medications can affect the blood flow on ONH. However, since the history of the hypertension medication and the number of glaucoma medication did not differ among groups in our study, this effect may not be great.

Finally, because CMvD is only identified within the β-PPA region in the OCT-A imaging, if the prevalence of PPA or β-PPA/disc ratio differed among groups, it could affect the identification of CMvD. The β-PPA/disc ratio did not differ among different types of glaucoma in our study. However, the PPA was less common in PACG than in POAG in the previous study. Thus, there can be a selection bias when we enrolled the subjects.

In conclusion, the prevalence of CMvD was significantly higher in POAG relative to PACG and PXG, especially in early-stage disease. This implies that CMvD could represent an ischemic mechanism of optic nerve damage in POAG. However, in the advanced disease group, the prevalence of CMvD increased in all 3 groups, and there was no difference between types of glaucoma. Hence, additional research will be needed to determine the clinical implications of CMvD in each type of glaucoma.

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