• Clinical Research •

Prevalence of focal lamina cribrosa defects in eyes with pachychoroid disease spectrum

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Abstract

● **AIM:** To determine the prevalence of focal lamina cribrosa (LC) defect among patients with pachychoroid disease spectrum (PDS) in the absence of peripapillary retinoschisis.

● **METHODS:** This retrospective, cross-sectional study comprised of 180 patients with PDS, including polypoidal choroidal vasculopathy (PCV), central serous chorioretinopathy, and pachychoroidal neovasculopathy. Medical records and optic nerve head evaluations conducted using spectral-domain optical coherence tomography with enhanced depth imaging were reviewed. As a control group, 236 patients who underwent ophthalmologic evaluation for vitreous floaters, without obvious ocular disease, were also included.

● **RESULTS:** The mean age of the PDS group, which included 118 male patients (65.6%), was 57.4±11.1y. There was no significant difference between the two groups in age (*P*=0.710) or sex (*P*=0.248). Six patients (3.3%) in the PDS group and none in the control group showed focal LC defect (*P*=0.318). Among the six patients with focal LC defect in the PDS group, four eyes had PCV, one eye was the fellow eye of a PCV eye, and one eye had pachychoroidal neovasculopathy.

● **CONCLUSION:** Focal LC defect can be defected in patients with PDS in the absence of peripapillary retinoschisis. However, the prevalence of focal LC defect was not different significantly between PDS patients and those who did not have PDS.

● **KEYWORDS:** central serous chorioretinopathy; lamina cribrosa; pachychoroid; polypoidal choroidal vasculopathy
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INTRODUCTION

Pachychoroid disease spectrum (PDS) is a recently defined clinical entities characterized by retinal pigment epithelium (RPE) abnormalities overlying areas of choroidal thickening[1-3]. PDS occurs due to pachychoroid-driven processes involving choroidal congestion and choroidal hyperpermeability, manifested in choroidal thickening and dilated choroidal vessels[1-3]. The current definition of PDS includes central serous chorioretinopathy (CSC), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy, and polypoidal choroidal vasculopathy (PCV).

A number of studies have shown disease characteristics, suitable treatment strategies, and possible pathogenesis of PDS, however, still various aspects of PDS such as optic nerve head (ONH) structures remain to be uncovered. A few studies have presented ONH structures in the PDS[4-5]. One study demonstrated that lamina cribrosa (LC) disinsertion or LC defect is associated with peripapillary retinoschisis in PDS as well as with glaucoma[4]. Increased leakage from the hyperpermeable choroidal vessels may lead to greater inflow of fluid to the ONH from the subarachnoid space through peripheral LC disinsertion or from the vitreous region through central LC defects in eyes with PDS; however, the study only included cases with PDS having peripapillary retinoschisis. Recently, one study defined peripapillary pachychoroid syndrome (PPS)[5] as a distinct variant of PDS, in which peripapillary choroidal thickening is associated with intraretinal and/or subretinal fluid in the nasal macula

and occasional ONH edema[5]. In that study, all eyes showed intraretinal fluid and cysts extending from the temporal disc margin, with associated atrophy of the RPE, photoreceptor ellipsoid zone, and external limiting membrane[5]. However, they suggested that peripapillary intraretinal fluid resembling peripapillary retinoschisis can occur in the eyes with PDS that do not show LC disinsertion[5].

Despite several studies have suggested the possible correlation of LC disinsertion/defect in the patients with PDS, there has been no study investigating the prevalence of focal LC defect among the patients with PDS. Based on these studies, we intended to examine the prevalence of focal LC defect among the patients with pachychoroid diseases, but without peripapillary retinoschisis. We also compared the prevalence of focal LC defects between the eyes with PDS in the absence of peripapillary retinoschisis and that of the normal control group.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Board of International St. Mary's Hospital and adhered to the tenets of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Enrollment of Study Subjects This retrospective, observational study was conducted at the Catholic Kwandong University College of Medicine, International St. Mary's Hospital. We reviewed the medical records of patients who were diagnosed with PDS and underwent ONH evaluation by enhanced depth imaging optical coherence tomography (EDI-OCT) between October 2017 and August 2019 retrospectively. Patients who underwent ophthalmologic evaluation for vitreous floaters but not presenting obvious ocular disease were included in the control group. During the study period, ONH evaluation by EDI-OCT was included in the routine ophthalmologic evaluation for testing purposes in our vitreoretinal clinic. The exclusion criteria were as follows: 1) eyes with glaucoma or history of intraocular pressure ≥22 mm Hg; 2) patients with family history of glaucoma; and 3) eyes with severe media opacity, for example caused by vitreous hemorrhage, which obscured EDI-OCT images of the retina and choroidal structures.

In the study group with PDS, CSC is characterized by choroidal congestion and choroidal hyperpermeability, which causesfocal RPE defects and serous pigment epithelial detachment[6-7]. PPE has features characteristic of RPE disturbances such as CSC, but lacks clinical or imaging evidence of acute or chronic subretinal fluid[1]. Pachychoroid neovasculopathy is a type-1 neovascularization that occurs in overlying focal areas of choroidal thickening in patients without a history of acute CSC and no evidence of chronic subretinal fluid, age-related macular degeneration, or other degenerative changes[2]. PCV is defined as the presence of abnormal branching vascular networks with polypoidal lesions shown by indocyanine green angiography[8-10].

The primary outcome measure was the prevalence of focal LC defect among patients with PDS in the absence of peripapillary retinoschisis.

Ocular Examination Ophthalmologic examination was performed for each patient according to our clinic's standard retinochoroidal evaluation procedure, as described previously[11-13]. Routine ophthalmologic evaluation included slit lamp examination, intraocular pressure measurement using a non-contact tonometer, and fundus examination after dilation. The refractive error was measured for each eye using an autorefractor followed by conversion to the spherical equivalent [diopters (D)]. For the diagnosis of CSC, PCV, and pachychoroidal neovasculopathy, fluorescein angiography and indocyanine green angiography were conducted with a Heidelberg Retina Angiograph System (HRA-2; Heidelberg Engineering, Heidelberg, Germany) with a confocal scanning laser ophthalmoscope.

Optical Coherence Tomography Evaluation of the Optic Nerve Head and Macula Spectral-domain optical coherence tomography (SD-OCT; Spectralis/Heidelberg Engineering) with EDI modality was used to examine the ONH and macula. For LC analysis, serial horizontal cross-sectional scans, approximately 30 μm apart and coering the ONH, were obtained (Figure 1A). EDI-OCT images of the ONH were reviewed by experienced glaucoma specialist (Lee NE), who was blinded to the retinal status; the presence of alterations in the LC was evaluated. Focal LC defect was defined as an anterior laminar surface irregularity violating the normal smooth curvilinear U- or W-shaped contour[13]. To avoid false-positives, defects needed to be >100 μm in diameter, >30 μm in depth, and present in at least one additional raster scan, as suggested by a previous study[14].

The mean subfoveal choroidal thickness (SFCT) was also measured using the Spectralis SD-OCT system with EDI. Choroidal thickness was defined as the perpendicular distance between the outer border of the hyperreflective line corresponding to the RPE, and the chorio-scleral interface[11-13]. For macular evaluation, serial cross-sectional horizontal scans were obtained, approximately 121 μm apart in a 30°×15° macular area[11-13]. Single horizontal and vertical scans across the fovea were acquired separately. To measure SFCT, at least two horizontal and vertical high-quality scans throughout the fovea were obtained from each eye. Utilizing the digital calipers in the Heidelberg Spectralis OCT software, the choroidal thickness was measured horizontally and vertically at the subfoveal region in each trans-sectional image, and the average measurement was calculated (Figure 1B). Three

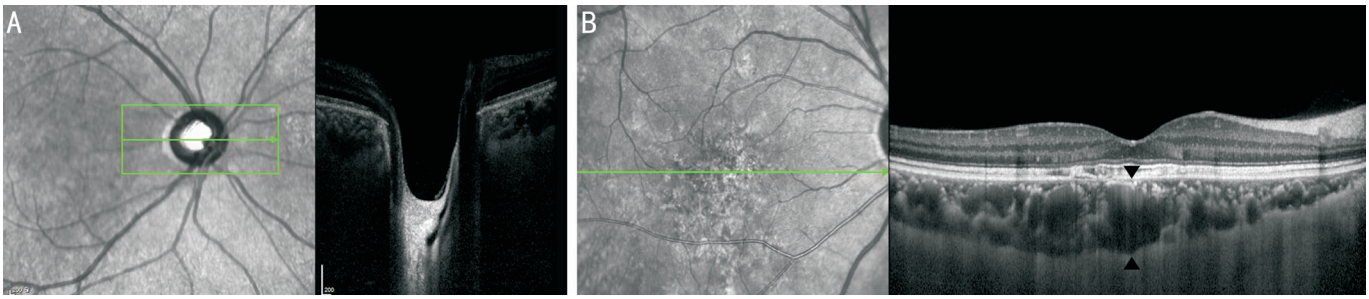

Figure 1 Representative image of the ONH and SFCT, obtained by SD-OCT with EDI (Spectralis) A: For the ONH assessment, serial horizontal cross-sectional scans, approximately 30 μm apart and covering the ONH, were obtained; B: Choroidal thickness was defined as the perpendicular distance from the outer border of the hyperreflective line demonstrating the RPE (upper arrowhead) to the chorio-scleral interface (lower arrowhead). Using digital calipers, SFCT was measured at the subfoveal region in both horizontal and vertical images; the two measurements were averaged.

Table 1 Comparison of clinical characteristics between patients with and without PDS mean±SD (range)

Characteristics	Patients with PDS (*n*=180)	Patients without PDS (*n*=236)	*P*
Age (y)	57.4±11.1 (34-80)	59.1±15.5 (32-78)	0.710[a]
Sex (male, %)	118 (65.6)	120 (50.8)	0.248[b]
Mean refractive errors (D)	1.1±0.8 (-1.5 to +2.25)	1.3±0.6 (-1.0 to +2.50)	0.870[a]
Mean cup/disc ratio	0.3±0.1 (0.2-0.4)	0.3±0.1 (0.2-0.4)	0.781[a]
Mean SFCT (μm)	401.5±148.2 (290.0-783.5)	253.0±80.5 (240.0-295.6)	<0.001[a]

PDS: Pachychoroid disease spectrum; SD: Standard deviation; SFCT: Subfoveal choroidal thickness. [a]Student's *t*-test and the [b]Chi-squared test were used for analyses of continuous and categorical variables, respectively. A *P*-value <0.05 was considered clinically significant.

independent observers (Kang HM, Lee NE, and Choi JH) blinded to the clinical data (including the ONH status of each patient) measured the choroidal thicknesses.

For statistical analysis, eyes with PDS, including CSC, PCV, and pachychoroid neovasculopathy, were included in the study. In cases with bilateral PDS eyes, the right eye was analyzed.

Statistical Analysis Unless indicated otherwise, data are presented as the mean±standard deviation (range). Baseline characteristics included age, sex, the cup/disc ratio, refractive error, and SFCT. IBM SPSS Statistics software for Windows (version 22.0; IBM Corporation, Armonk, NY, USA) was used for the statistical analyses. Student's *t*-test and the Kruskal-Wallis test were used for analyzing continuous variables and the Chi-square test was used for the analysis of categorical variables. Mauchly's test of sphericity and Kolmogorov-Smirnov analyses were also applied. *P*-values <0.05 were considered statistically significant.

RESULTS

Clinical Characteristics of the Study Population We retrospectively reviewed 180 consecutive patients with PDS and 236 patients without PDS, who met the study criteria. Among the patients with PDS, 118 (65.6%) were male and the mean age at the time of examination was 57.4±11.1y (range: 34-80y). There were no significant differences in clinical characteristics between the patients with PDS and the control group, including age (*P*=0.710) and sex (*P*=0.248). The mean SFCT was significantly higher in the PDS group than in the control group (*P*<0.001). A detailed comparison of the clinical characteristics between the two groups is shown in Table 1.

Among the patients with PDS, the primary diagnosis was CSC in 73 (40.6%), PCV in 75 (41.7%), and pachychoroidal neovasculopathy in 32 (17.8%); all patients underwent intravitreal anti-vascular endothelial growth factor injections.

Alteration of Lamina Cribrosain Patients with and Without Pachychoroid Spectrum Diseases Among 180 patients with PDS, 6 (3.3%) showed focal LC defects in the absence of peripapillary retinoschisis. No patients in the control group showed focal LC defect. Diabetic retinopathy (DR) was not observed in any patient. The prevalence of focal LC defect was not significantly different between patients with and without PDS (*P*=0.318). Among the six patients with PDS and focal LC defects, four eyes had PCV, one eye was the fellow eye of the PCV eye, and one eye showed pachychoroidal neovasculopathy. The detailed characteristics of the six patients with focal LC defects are listed in Table 2, and representative images are shown in Figures 2-6.

DISCUSSION

In this study, we examined the prevalence of focal LC defect patients with PDS in the absence of peripapillary retinoschisis; six patients (3.3%) showed focal LC defect. Although the majority of focal LC defect occurred in active PDS-affected eyes, focal LC defect was also found in the contralateral eye

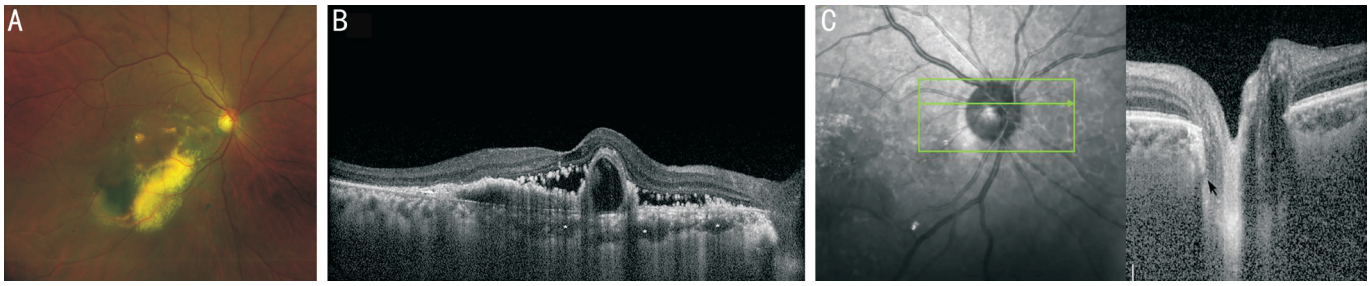

Figure 2 Representative image of a 62-year-old female patient (Patient 1) with PCV in the right eye A: Subretinal fluid with exudates and hemorrhage involving the macula of the right eye, shown by ultrawide fundus photography; B: Spectral domain optical coherence tomography revealed fibrovascular pigment epithelial detachment with subretinal fluid and exudates; dilated choroidal vessels were noticeable (asterisk); C: Focal LC defect was detected during ONH evaluation (arrow head).

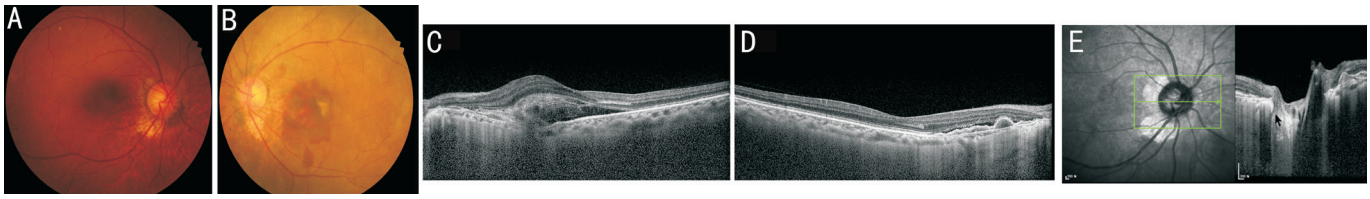

Figure 3 Representative image of a 78-year-old female patient (Patient 2) with PCV in both eyes PCV, which first occurred in the left eye, was treated by intravitreal bevacizumab injections; 23mo later, PCV recurred in the left eye along with subretinal fluid. A: Peripapillary chorioretinal atrophy with adjacent prominent choroidal vasculature in the right eye. B: Subretinal hemorrhage with exudates in the left eye. C: SD-OCT of the left eye showed fibrovascular pigment epithelial detachment with subretinal hemorrhage, exudates and fluid. D: Twenty-three months after the first visit, subretinal fluid developed in the right eye, as indicated by SD-OCT. E: Focal LC defect (arrow head) in the right eye was detected during ONH evaluation.

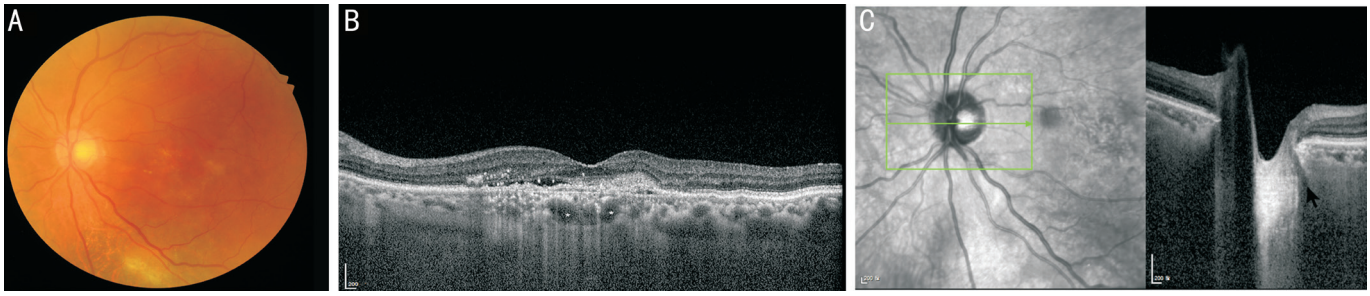

Figure 4 Representative image of a 79-year-old male patient (Patient 3) with PCV in the left eye The patient had disciform scarring in the right eye. A: Subretinal exudative fluid with foveal involvement was noted on fundus photography. Chorioretinal atrophy was evident from the inferior to inferotemporal vascular arcade. B: SD-OCT revealed a fibrovascular membrane with subretinal fluid. Dilated choroidal vessels were noticeable (asterisk). C: Focal LC defect was detected during ONH evaluation (arrow head).

Table 2 Detailed characteristics of the six patients with PDS and focal LC defects

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (y)	62	78	79	56	44	68
Sex	Female	Female	Male	Male	Male	Male
Systemic diseases	HTN	DM, HTN	BPH	None	None	HTN
Primary diagnosis	PCV	PCV	PCV	PCV, hemorrhagic	Pachychoroidal neovasculopathy	PCV
Status of fellow eye	PPE	PCV	Disciform scar	PPE	PPE	PPE
Presence of LC disinsertion	Affected eye	Affected eye	Affected eye	Contralateral eye	Affected eye	Affected eye
Mean SFCT (μm)						
LC disinsertion	224.0	250.0	229.0	226.5	351.0	368.0
Non-LC disinsertion	187.5	153.5	227.5	329.5	348.0	341.0

DM: Diabetes mellitus; HTN: Hypertension; LC: Lamina cribrosa; PCV: Polypoidal choroidal vasculopathy; PPE: Pachychoroid pigment epitheliopathy; SFCT: Subfoveal choroidal thickness.

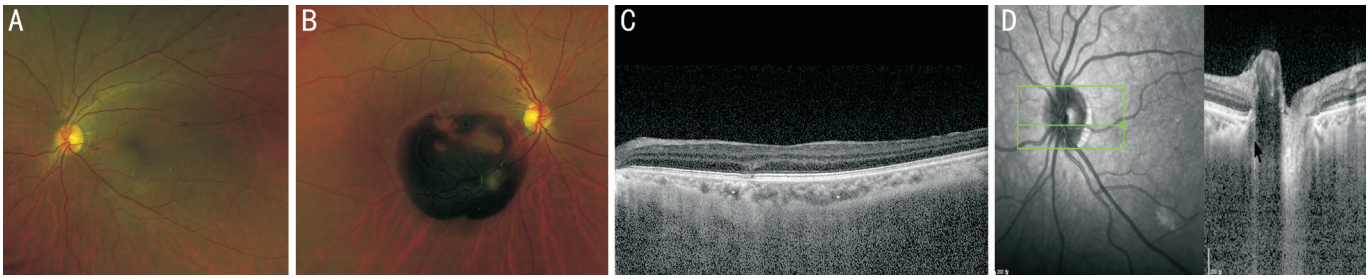

Figure 5 Representative images of the left eye of a 56-year-old patient with pachychoroid pigment epitheliopathy (Patient 4) A: Tigroid fundus with prominent choroidal vasculature in the left eye; B: The contralateral right eye showed massive subretinal hemorrhagic detachment, associated with PCV; C: Dilated choroidal vessels and mild photoreceptor disruption without subretinal fluid were observed in the left eye using SD-OCT; D: ONH evaluation showed focal LC defect in the left eye (arrow head).

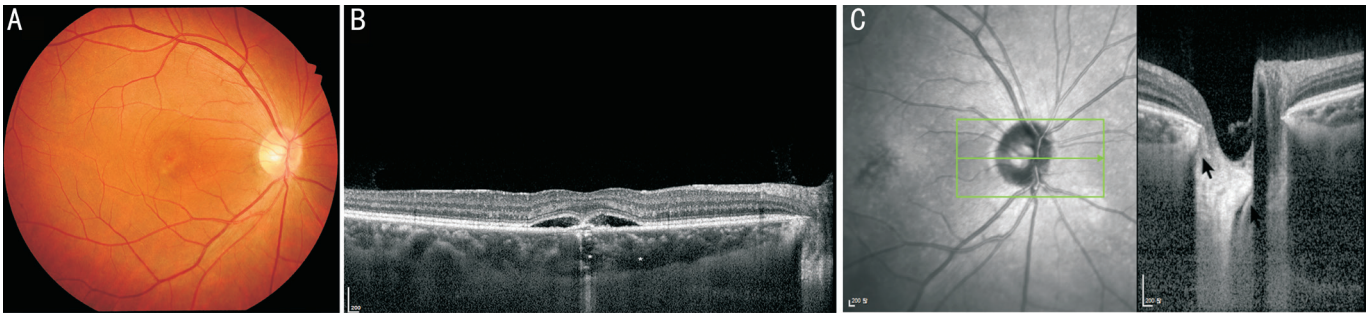

Figure 6 Images of a 44-year-old male patient with pachychoroid neovasculopathy in the right eye (Patient 5) A: Subretinal turbid fluid with depigmentation involving the fovea was noted on fundus photography. B: SD-OCT showed fibrovascular pigment epithelial detachment with subretinal fluid involving the foveal center. Dilated choroidal vessels were noticeable (asterisk). C: ONH evaluation showed focal LC defect (arrow head).

of ahemorrhagic PCV. However, further comparison showed no significant difference in the prevalence of focal LC defect between patients with and without PDS.

It has been suggested previously that hydrostatic pressure leads to LC disinsertion/defect in PDS[4-5,15-18]. Based on this hypothesis, we assumed that LC disinsertion/defect and subsequent peripapillary retinoschisis may reflect higher hydrostatic pressure, disease activity, and further treatment response.

However, based on our findings, we discarded the primary hypothesis that increased hydrostatic pressure of PDS may be associated with development of LC disinsertion/defect. At least the eyes with PDS but without peripapillary retinoschisis, it seems that increased hydrostatic pressure does not have significant impact on the development of LC alteration. Simply, the presence of focal LC defect among the patients with PDS may be just accidental findings of normal ONH variants in this study.

Previously, our study group investigated the prevalence of focal LC defects in the patients with unilateral branch retinal vein occlusion (BRVO), those with normal tension glaucoma (NTG), and the normal control group[19]. In that study, prevalence of focal LC defects were significantly higher in the eyes with BRVO and those with NTG than that of the normal control group: the prevalence of focal LC defects was 38.9% in the BRVO group, 41.7% in the NTG group, and none in the control group[19]. In addition, the mean peripapillary choroidal thickness was significantly thinner in the eyes with focal LC defects than those without in both the BRVO group and the NTG group. Based on these results, our study group assumes the possible pathophysiologic correlation between BRVO and NTG. Although this study lacks of the NTG group, we could infer that focal LC defects in the patients with PDS may not be significantly correlated with pathologic changes of ONH, because there was no significant difference in the prevalence of focal LC defects between the PDS group and the normal control group.

If focal LC defect in the eyes with PDS but without peripapillary retinoschisis is simply one of the normal ONH variants, there would be no significant impact of focal LC defect on disease activity and treatment response in the patients with PDS. However, we cannot confirm the underlying pathogenesis of focal LC defects in patients with PDS based on the results of this cross-sectional study, where it was difficult to determine the precise time at which focal LC defects occurred in the PDS patients. If focal LC defect is one of normal ONH variants, it may be observed before disease onset. Further studies on peripapillary structures are

necessary to broaden our understanding of PDS. In addition, further longitudinal studies on the association between focal LC defects and the development of peripapillary retinoschisis may provide more insight to this structural change of ONH in PDS. Thus, we suggest that future investigations examine peripapillary choroidal structures and determine ONH status in patients with PDS.

Our study had several limitations, including a relatively small study population. Moreover, due to the retrospective nature of the study, the control group was relatively heterogeneous. Further investigations with larger populations, a longitudinal design should enhance our understanding of LC disinsertion in patients with PDS.

Although our study has several limitations, our study is the first attempt to investigate the prevalence of focal LC defects in the patients with PDS but without peripapillary retinoschisis. We could assume that the presence of focal LC defect in the patients with PDS but without peripapillary retinoschisis is accidental finding of normal ONH variants, rather than pathophysiological change associated with increased hydrostatic pressure.

In conclusion, focal LC defect was observed in patients with PDS in the absence of peripapillary retinoschisis, in both diseased eyes and disease-free contralateral eyes. However, the prevalence of LC disinsertion was not significantly different between patients with PDS and the control group.

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Authors' contributions: Kang HM designed and conducted the study. Kang HM, Lee NE, and Choi JH collected the data. Kang HM, Lee NE, Choi JH, Koh HJ, and Lee SC managed, analyzed, and interpreted the data. Kang HM, Lee NE, Choi JH, Koh HJ, and Lee SC prepared, reviewed, and approved the manuscript.

Conflicts of Interest: Kang HM, None; **Lee NE,** None; **Choi JH,** None; **Koh HJ,** None; **Lee SC,** None.

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