Polypoidal Choroidal Vasculopathy: Outer Retinal and Choroidal Changes and Neovascularization Development in the Fellow Eye

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PURPOSE. We investigated the outer retinal, RPE, and choroidal changes and the development of choroidal neovascularization (CNV) in fellow eyes of patients with unilateral polypoidal choroidal vasculopathy or aneurysmal type 1 neovascularization (PCV/AT1).

METHODS. In this retrospective observational cohort study, 263 patients with unilateral PCV/AT1 were enrolled. Fundus photography, enhanced depth imaging optical coherence tomography, and indocyanine green angiography at baseline and follow-up were analyzed. Incidence and risk factors for the development of CNV were analyzed.

RESULTS. In fellow eyes of unilateral PCV/AT1 cases, RPE and outer retinal abnormalities were observed in 222 (84%) eyes, and dilated Haller vessels (pachyvessel) were identified in the corresponding abnormality area in 157 (71%) eyes. Follow-up data were available for 233 patients. During a 27.6-month mean follow-up period, 20/233 (9%) eyes had CNV (12 PCV/AT1 and eight type 1 CNV). In 18 eyes (90%), CNV developed at the RPE or outer retinal corresponding abnormality area accompanied by pachyvessel. A significantly higher risk for CNV was observed if RPE and outer retinal abnormalities were accompanied by pachyvessel (hazard ratio, 9.3; 95% confidence interval, 1.1–75.9, P = 0.037).

CONCLUSIONS. RPE and outer retinal abnormalities were common in fellow eyes of patients presenting with unilateral PCV/AT1. CNV developed in fellow eyes of 9% of patients, frequently in the areas with RPE and outer retinal abnormality accompanied by pachyvessel.

Keywords: polypoidal choroidal vasculopathy, fellow eye study, RPE changes, pachyvessel, incidence

Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi et al.1 as polypoidal, subretinal, vascular lesions associated with serous and hemorrhagic detachments of the RPE. Imaging and histologic evidences revealed that the polypoidal structure resulted from a vascular dilatation rather than a fleshy mass. Therefore, recently, the nomenclature of choroidal neovascularization (CNV) in fellow eyes of patients with unilateral polypoidal choroidal vasculopathy or aneurysmal type 1 neovascularization (PCV/AT1).

Traditional indocyanine green angiography (ICGA) has revealed that choroidal vascular hyperpermeability and dilated choroidal vessels are characteristic findings in central serous chorioretinopathy (CSC) and PCV/AT1, indicating that choroidal circulatory disturbance has a significant pathophysiologic role.21 Recent advances in optical coherence tomography (OCT) imaging have enabled detailed evaluation of changes within the choroid and RPE. Not only increased thickness of the total choroid, but also the peculiar morphology of the dilated Haller vessel with choriocapillaris attenuation and changes in the overlying RPE and outer retina has been increasingly recognized as a potential precursor for serous change or choroidal neovascularization (CNV) in these eyes.22–25
The prevalence of bilateral disease in patients with PCV/AT1 has been reported to range from 6% to 24% in Asians.4–6,26 However, there is currently limited information on the characteristics and longitudinal changes in the fellow eyes of patients presenting with unilateral PCV/AT1. Few longitudinal studies have reported the incidence of CNV in these eyes. Therefore, we assessed the morphologic characteristics of the fellow eyes in cases of unilateral PCV/AT1, focusing on the choroid and related RPE and outer retinal abnormalities using enhanced depth imaging (EDI), spectral domain OCT, and ICGA to document common background pathophysiologic changes in these eyes. In addition, CNV development rate in fellow eyes and related risk factors were analyzed to identify preceding pathology, which might give hints regarding PCV/AT1 pathogenesis.

METHODS

Patients

This retrospective cohort study was performed at the Department of Ophthalmology in Seoul St. Mary’s Hospital, The Catholic University of Korea (Seoul, Korea). The study was approved by the institutional review board of Seoul St. Mary’s Hospital and conducted according to the Declaration of Helsinki.

We reviewed the medical records of 361 patients diagnosed with PCV/AT1 between November 2011 and January 2016. A PCV/AT1 diagnosis was established if the characteristic vascular lesions, including polypoidal dilatation with or without a branching vascular network (BVN), were noted on ICGA. For the purpose of analysis, we only included patients presenting with unilateral PCV/AT1 (defined as absence of a late ICGA hotspot or plaque in the fellow eye, with or without exudative change). Patients with conditions that could affect RPE and choroidal morphologic changes (e.g., history of systemic steroid use and other concurrent diseases, including diabetic retinopathy, uveitis, or tumors) and with a history of anti-VEGF treatment, prior laser or photodynamic therapy, retina or choroid trauma, and a spherical equivalent refractive error greater than 6diopters in the fellow eye were excluded.

All patients underwent comprehensive ophthalmologic examinations in both eyes at baseline: best-corrected visual acuity (BCVA) testing, fundus examination with slit-lamp biomicroscopy and color fundus photography, OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) with an EDI protocol, ICGA, and fluorescein angiography (FA). Snellen visual acuity was converted to logMAR for statistical analysis.

Analysis of Drusen and Pachydrusen in Both Eyes

The presence of reticular pseudodrusen, drusen, and pachydrusen was assessed on color fundus photography in both eyes. These findings were confirmed on OCT images by point-to-point correlation. The definitions of drusen and reticular pseudodrusen followed those used in previous reports.27,28 Pachydrusen were considered present if there were isolated or scattered yellowish white deposits on color fundus photographs, which were distinctive from drusen or reticular pseudodrusen (i.e., single or clusters of drusen that have a characteristic shape with a complex and irregular contour and a better-defined border) that corresponded to the presence of homogeneous material accumulation under RPE on OCT images (Fig. 1).23,29,30

RPE Changes and Outer Retinal Abnormalities in the Fellow Eye

RPE changes on OCT images were defined as ‘irregular undulation’ (Fig. 2A), ‘inward bowing’ of RPE and Bruch’s membrane complex (Fig. 2B), and ‘focal defect’ (Fig. 2C). The presence of pigment epithelial detachment (PED) was recorded (Fig. 2D). Outer retinal abnormalities, including ellipsoid zone (EZ)/interdigitation zone (IZ), and external limiting membrane (ELM) defect were also analyzed (Fig. 2E).

Analysis of Choroidal Features in Both Eyes

We assessed the presence/absence of pachyvessel based on 25-line horizontal raster EDI OCT scans using methods described previously, and further evaluated their location in relation to the area where BVN originated on ICGA.31 In the fellow eye, pachyvessel was defined as a dilated Haller vessel accompanied with overlying choriocapillaris attenuation that was localized under RPE and/or outer retinal abnormalities. Pachyvessel presence on OCT was confirmed by the presence of a corresponding dilated large choroidal vessel on ICGA imaging. Choroidal thickness was measured using a previously described method by two experienced EDI OCT imaging graders (J.B. and J.H.L).32 The average measurements of the two observers were used for analysis. Measurements were performed subfoveally and at the thickest point of the pachyvessel area in both eyes. Choroidal vascular hyperpermeability, defined as multifocal areas of hyperfluorescence with blurred margins within the choroid, also was assessed on late phase ICGA images.31

Evaluation of Longitudinal Changes in the Fellow Eye

In patients for whom follow-up data were available, serial OCT images were assessed for identifiable changes in any of the aforementioned parameters. FA and ICGA were taken when newly developed hemorrhage or exudative changes were observed to confirm the diagnosis for CSC, CNV, or PCV/AT1.
CNV was defined as any vascular network visible on ICGA with active leakage on the corresponding area on FA or any fluid accumulation and/or hemorrhage on OCT. If there was no visible polyp, it was defined as PCV/AT1.

Statistical Analysis
Statistical analyses were performed using SPSS statistical software (version 19.0; SPSS Inc., Chicago, IL, USA). To compare affected eyes and fellow eyes, a $\chi^2$ test for categorical variables was used. A paired t-test was used for continuous variables. CNV incidence in the fellow eye was calculated using a Kaplan-Meier survival analysis. To investigate risk factors for CNV development in fellow eyes, univariate analysis was followed by multivariate analysis using Cox regression. The hazard ratio (HR) and 95% confidence interval (CI) for the Cox proportional hazard models were calculated. $P < 0.05$ was considered statistically significant.

RESULTS
Baseline Characteristics of the Affected and Fellow Eyes
Of 361 patients diagnosed with PCV/AT1, 78 (22%) bilateral patients and 20 (6%) without bilateral baseline examination were excluded. Thus, 263 patients with unilateral PCV/AT1 were enrolled in the study. Mean age was 65.1 ± 8.0 years (range, 39–87 years), and 188 (71%) patients were male. A total of 18 (7%) patients had a history of CSC in the affected eye. Mean logMAR BCVA was 0.50 (range, 39–87 years), and 188 (71%) patients were male. A total of 20 eyes (9%) had CNV (12 PCV/AT1 and 8 type 1 CNV; Figs. 5, 6) and two (1%) had CSC. The follow-up period was similar between eyes with and without CNV (30.2 ± 14.4 vs. 27.3 ± 15.5 months, $P = 0.413$). Comparison between these eyes revealed that the presence of irregular undulation of RPE, PED, and pachyvessel at baseline was significantly associated with development of CNV (Table 2). In 18 eyes (90%), CNV developed at the area of RPE or outer retinal abnormality areas accompanied by pachyvessel.

Univariate Cox regression risk factor analysis revealed that RPE irregular undulation, PED, presence of pachyvessel, and the total number of abnormalities were significant risk factors for development of CNV in the fellow eye (Table 3). PED and pachyvessel presence remained as significant risk factors in multivariate Cox regression analysis.

Choroidal Morphology
Pachyvessels were identified in 258 (98%) affected and 157 (60%) fellow eyes ($P < 0.001$). Choroidal thickness at the subfovea and pachyvessel area did not differ between the affected and fellow eyes ($P = 0.239$ and 0.366, respectively). The ratio of Haller's layer thickness to total choroid was higher in the affected eye compared to the fellow eye at the subfovea and pachyvessel areas ($P < 0.001$ and $P = 0.004$, respectively). Choroidal thickness and the Haller's layer proportion were higher in the pachyvessel area compared to the subfoveal location in the affected and fellow eyes (all $P < 0.001$). The presence of choroidal vascular hyperpermeability did not differ between the affected and fellow eyes ($P = 0.088$; Table 1).

Longitudinal Changes and Risk Factors for Neovascularization in the Fellow Eye
Follow-up data for fellow eyes were available in 233 patients. Mean follow-up period was 27.6 ± 15.5 months (range, 4–62 months). Changes of pre-existing pachydrusen, RPE irregular undulation, PED progression, and EZ/IZ defect were observed in 10 (4%), two (1%), two (1%), and three (1%) eyes, respectively. RPE irregular undulation, EZ/IZ defect, and PED developed in two (1%), one (0%), and eight (3%) eyes, respectively. Development of Peripapillary retinoschisis was identified in two (1%) eyes (Fig. 3). Spontaneous healing of preexisting RPE or EZ/IZ defect was observed in two (1%) eyes (Fig. 4).

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FIGURE 2. RPE and outer retinal abnormalities identified in fellow eyes of PVC by OCT. (A) RPE ‘irregular undulation’ was defined as irregular undulation of the RPE band with flat PED. (B) RPE ‘inward bowing’ was defined as convex or concave RPE bowing in conjunction with underlying focal choroidal thickening. (C) RPE ‘focal defect’ was defined as partial or full thickness RPE band defect. (D) PED was recorded using the conventional definition of serous PED (i.e., an area of sharply demarcated, dome-shaped serous elevation of the RPE not associated with CNV or drusen). Yellow arrowhead indicates Bruch’s membrane. (E) The presence of EZ/IZ and/or outer limiting membrane defect also was assessed. White arrows indicate RPE and outer retinal abnormalities, and arrowheads indicate pachyvessels under the lesion.
DISCUSSION

The changes in RPE and outer retina associated with aging, which involves hypoxia and oxidative stress, are well-documented pathophysiologic processes in the early stages of typical AMD. These changes often present in the form of drusen.33-35 Traditional risk factors for typical AMD are Age-Related Eye Disease Study (AREDS) score (based on drusen and pigmentary changes), RPE elevation, and hypertension.36,37 However, there is limited information on RPE and associated outer retinal changes in earlier stages, and little is known on the risk factors for neovascularization in PCV/AT1, which

<table>
<thead>
<tr>
<th>Choroidal Profiles</th>
<th>PCV Eyes</th>
<th>Fellow Eyes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of pachyvessel under lesion, n (%)</td>
<td>258 (98)</td>
<td>157 (60)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Choroidal vascular hyperpermeability, n (%)</td>
<td>75 (29)</td>
<td>58 (22)</td>
<td>0.088</td>
</tr>
<tr>
<td>Choroidal thickness, mean ± SD (range)</td>
<td></td>
<td></td>
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<tr>
<td>Subfovea</td>
<td></td>
<td></td>
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<tr>
<td>Total choroidal thickness, μm</td>
<td>253 ± 114 (62-624)</td>
<td>258 ± 113 (50-657)</td>
<td>0.239</td>
</tr>
<tr>
<td>Haller's layer thickness, μm</td>
<td>188 ± 91 (40-559)</td>
<td>185 ± 93 (35-586)</td>
<td>0.559</td>
</tr>
<tr>
<td>Ratio of Haller's layer to total thickness</td>
<td>0.74 ± 0.09 (0.45-0.95)</td>
<td>0.71 ± 0.10 (0.38-0.94)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pachyvessel area, n = 157</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total choroidal thickness, μm</td>
<td>297 ± 108 (100-679)</td>
<td>305 ± 105 (76-771)</td>
<td>0.366</td>
</tr>
<tr>
<td>Haller's layer thickness, μm</td>
<td>269 ± 101 (86-615)</td>
<td>271 ± 98 (66-677)</td>
<td>0.87</td>
</tr>
<tr>
<td>Ratio of Haller's layer to total thickness</td>
<td>0.91 ± 0.04 (0.73-0.98)</td>
<td>0.88 ± 0.05 (0.71-0.98)</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

* Statistically significant P value.

FIGURE 3. Longitudinal changes of the RPE and outer retinal abnormalities in fellow eyes of PCV. (From left to right) Fundus color photography, mid-phase ICGA, baseline and follow-up OCT images. (A) Fellow eye of a 60-year-old male. Subretinal fluid developed at the outer retinal area and RPE abnormalities (arrows) overlying pachyvessel (arrowheads) with choriocapillaris attenuation after 1 year of follow-up. (B) Fellow eye of a 58-year-old male. Pachyvessels (arrowheads) with choriocapillaris attenuation are observed under diffuse RPE irregular undulation. Follow-up OCT demonstrated pigment epithelial detachment (arrow) progression and newly developed peripapillary retinoschisis in both (thick arrows). (C) Fellow eye of a 51-year-old male. The EZ/IZ defect developed at the RPE undulation (arrows) area overlying pachyvessels (arrowheads) with choriocapillaris attenuation after 2 years of follow-up. (D) Fellow eye of a 67-year-old male. A pachydrusen (arrow) was observed over the pachyvessel area at baseline. Fourteen months later, irregular RPE undulation developed at the previous pachydrusen (arrow) area.
rarely presents with drusen. Recently, the role of the choroid is increasingly emphasized in the pathogenesis of PCV/AT1.22–23 To our knowledge, this is the first longitudinal study to report choroidal changes associated with retinal changes that might be related to the PCV/AT1 pathogenesis.

Our results showed that drusen and reticular pseudodrusen are relatively uncommon in the fellow eyes of unilateral PCV/AT1, as in the affected eyes. This is in accordance with what already is known, and it is an important difference compared to typical AMD.8,29 In contrast, pachydrusen were observed in higher percentages of affected and fellow eyes. The histopathologic nature of pachydrusen remains unknown, but the accumulation of any material below the RPE poses a possibility of some degree of RPE dysfunction.

Other RPE and outer retinal changes have been observed in eyes with pachychoroid spectrum diseases.25,38–40 In a fellow eye study of CSC, RPE alteration was seen in 94% fellow eyes.41 These changes were observed in 84% of PCV/AT1 fellow eyes in our study. RPE irregular undulation in this study, which was identified in 64% fellow eyes, encompasses a wide range of RPE deformities - from RPE aggregation as in acute retinal pigment epitheliitis or as in a primitive form of pachydrusen, to shallow irregular PEDs.40,42–44 While the resolution of current OCT imaging devices does not always permit differentiation of RPE irregular undulations, a histopathologic study by Curcio et al.45 revealed the detailed structure in type 1 neovascularization (type 1 NV). Type 1 NV, which appeared as shallow irregular PED on OCT, was composed of multiple layers of anatomic framework that includes fibrovascular membrane, intact RPE, and Bruch’s membrane in high resolution histologic images. Considering that PCV may arise from type 1 NV, RPE irregular undulation, which had a role as a precursor for PCV/AT1 in this study, may have similar histology.

EZ/IZ defects were observed more commonly than RPE defects (40% vs. 20%). In a histologic study of PCV/AT1, choriocapillaris are attenuated or absent under the lesion as even in eyes in which RPE had been preserved.46 The outer one-third of the retina (i.e., photoreceptors and RPE) receives its oxygen and nutrient supply from the choroidal circulation. Considering topographic relationships, early stages of ischemic change following choroidal circulation disturbance can be limited to photoreceptors that are more distant from choriocapillaris, thereby causing EZ/IZ abnormality before any RPE change. However, further studies using imaging modalities that are more sensitive to RPE change, such as fundus autofluorescence or polarization-sensitive OCT, are required to confirm this hypothesis.

Choroidal vasculature is another remarkable difference between PCV/AT1 and typical AMD. Dansingani et al.38 reported that pachyvessels occupied the full choroid thickness with loss of overlying Sattler’s and choriocapillaris layers in pachychoroid spectrum diseases. These characteristic choroidal features also were observed even in PCV/AT1 eyes with thin choroid.31 In this study, pachyvessels were observed in 60% of fellow eyes. The proportion of the Haller’s layer was higher in the affected compared to the fellow eye, suggesting there is further attenuation of the choriocapillaris in the process of PCV/AT1 development. Additionally, pachyvessel can cause mechanical stress to the RPE as demonstrated by RPE stretching in a way similar to that in which Haller vessels can cause RPE atrophies in highly myopic eyes.47 Based on these findings, we suppose that choriocapillaris impairment associated with the pachyvessel is an important background pathophysiology in the earlier RPE and outer retinal changes of PCV/AT1.

We also analyzed the incidence and associated risk factors for CNV development in the fellow eye. The identified risk factors for CNV were PED and pachyvessel presence. Pachyvessel together with RPE and/or outer retinal abnormalities may constitute the environmental antecedent to CNV development. However, the causal relationship between them remains to be elucidated. Conventionally, choroid modification is considered to be a response to alteration of RPE and Bruch’s
membrane complex rather than representing intrinsic change in typical AMD. Later studies evidenced decreased choriocapillaris density associated with the aging process itself or despite intact Bruch’s membrane. Therefore, the possibility that choroidal changes occur independently of changes in other tissues cannot be excluded.

Among 20 newly developed fellow eye CNVs, 12 were PCV/AT1 and eight were type 1 CNV in which no definite polyp was identified. It has been suggested that patients with pachychoroid epitheliopathy may suffer type 1 CNV, which can progress to PCV/AT1. In one previous study on fellow eye neovascularization in PCV/AT1, late geographic ICGA hyperfluorescence that corresponded with or included BVN bounds was identified as a risk factor and four eyes suffered nonpolypoidal exudative CNV. This further indicates that polyp development can be a change secondary to preexisting choroidal angiographic changes, including BVN, especially when polypoidal structure is an aneurysmal change that occurs at pre-existing vasculatures. In this study, 11 fellow eyes showed direct PCV/AT1 development without preexisting type 1 CNV or longstanding CSC. Mean follow-up time to CNV development did not differ between PCV/AT1 and type 1 CNV. These results implied that PCV/AT1 and pachychoroid neovascularopathy may share a common pathogenic mechanism and a polypoidal structure (aneurysm) can develop in the earlier stage or later depending on genetic and environmental influences.

This study has several limitations. Standardized data could not be obtained owing to its retrospective design. Fundus autofluorescence, which is a sensitive imaging modality to evaluate RPE changes, was not included, leaving the possibility for missing subtle RPE changes. In longitudinal change analysis, selection bias is likely to be caused by excluding patients for whom follow-up data were not available. Finally, with imaging advances, shallow irregular PEDs were identified as type 1 CNV on OCT angiography in many cases. RPE irregular undulations in this study may contain an early quiescent CNV form that was not detected on ICGA. Because the development of CNV in this study was defined only when exudative changes were observed, the actual incidence of quiescent CNV may be

<table>
<thead>
<tr>
<th>Findings</th>
<th>Eyes Without CNV, n = 213</th>
<th>Eyes With CNV, n = 20</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drusenoid lesions, n (%)</td>
<td>56 (26)</td>
<td>7 (35)</td>
<td>0.609</td>
</tr>
<tr>
<td>RPE abnormalities</td>
<td></td>
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<tr>
<td>RPE irregular undulation, n (%)</td>
<td>131 (62)</td>
<td>18 (90)</td>
<td>0.004*</td>
</tr>
<tr>
<td>RPE inward bowing, n (%)</td>
<td>59 (28)</td>
<td>3 (15)</td>
<td>0.261</td>
</tr>
<tr>
<td>RPE defect, n (%)</td>
<td>42 (20)</td>
<td>7 (35)</td>
<td>0.078</td>
</tr>
<tr>
<td>PED, n (%)</td>
<td>20 (9)</td>
<td>5 (25)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Outer retinal abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZ/IZ defect, n (%)</td>
<td>85 (40)</td>
<td>10 (50)</td>
<td>0.272</td>
</tr>
<tr>
<td>ELM defect, n (%)</td>
<td>28 (13)</td>
<td>5 (29)</td>
<td>0.113</td>
</tr>
<tr>
<td>Abnormalities accompanied with pachyvessel, n (%)</td>
<td>122 (57)</td>
<td>18 (90)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Number of eyes with any abnormalities, n (%)</td>
<td>179 (84)</td>
<td>19 (95)</td>
<td>0.200</td>
</tr>
<tr>
<td>Number of abnormalities per eye, mean ± SD</td>
<td>2.5 ± 1.8</td>
<td>3.5 ± 1.9</td>
<td>0.021</td>
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* Statistically significant P value.
higher. A longitudinal study using OCT angiography is needed. Additionally, the object of this study included an Asian population only; therefore, generalization of our results required validation in other ethnic groups. However, this study included longitudinal observation of changes in unaffected fellow eyes that involved a relatively large sample size in a homogeneous ethnic group in which disease prevalence is high. In addition, while the measurement of choroidal thickness was limited to the subfovea in most studies, we also analyzed the choroid at the disease focus. By analyzing choroidal layers, we were able to give more specific information on the choroidal feature. We believe that these results are valuable for explaining disease pathogenesis and for prediction of changes in PCV/AT1 fellow eyes.

The CNV pathogenetic process involves changes in the choroid, Bruch’s membrane, RPE, and outer retina, but there is doubt as to which tissues are primarily affected by these factors. In typical AMD, the initial step is considered to be changes in the RPE and Bruch’s membrane that accumulate with senescence. However, in PCV/AT1, which seems less involved with the aging process, the initial change may be different. In this study involving 263 Asian patients with PCV/AT1, we found that RPE and outer retinal abnormalities were common in PCV/AT1 fellow eyes. The changes frequently were accompanied by choroidal pachyvessel, which was a risk factor for CNV development. Further studies are warranted to clarify the cumulative effects of these changes as well as genetic and environmental influences in PCV/AT1 pathogenesis.

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