Reticular Pseudodrusen
A Risk Factor for Geographic Atrophy in Fellow Eyes of Individuals with Unilateral Choroidal Neovascularization

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Purpose: To determine whether reticular pseudodrusen (RPD) confer an increased risk of progression to late-stage age-related macular degeneration (AMD) in fellow eyes of those recently diagnosed with unilateral choroidal neovascularization (CNV).

Design: Retrospective study.

Participants: Two hundred consecutive participants with CNV secondary to AMD in 1 eye and no signs of late-stage AMD in the fellow eye.

Methods: Clinical examination and comprehensive retinal imaging, including spectral-domain optical coherence tomography, near-infrared reflectance (NIR), and color fundus photography, at baseline and every follow-up visit.

Main Outcome Measures: Incidence of geographic atrophy (GA) and CNV in the fellow eye.

Results: Mean age ± standard deviation was 77±7 years, and 61% of the cohort were female. Fifty-eight percent (n = 116) had RPD, 68% had drusen of 125 μm or more, 36% had pigmentary changes, 10% had both drusen of 125 μm or more and pigmentary changes, and 17% had only RPD in their fellow eyes. After a mean follow-up of 2.3 years, CNV developed in 36% of patients and GA developed in 14% of patients. Those with RPD demonstrated late-stage AMD (61% vs. 33.4%; P < 0.001) and GA (22.4% with RPD vs. 2.4% without RPD; P < 0.001) more often. The presence of reticular pseudodrusen was an independent risk factor for the development of GA (hazard ratio [HR], 4.93; P = 0.042), but not for CNV (HR, 1.19; P = 0.500), at least within the follow-up of this study. Both drusen of 125 μm or more and pigmentary changes at baseline were significant risk factors for the development of CNV and GA (HR, 1.96–11.73; P ≤ 0.020).

Conclusions: Reticular pseudodrusen seem to confer an increased risk of progression to GA, in addition to drusen and pigmentary changes. The presence of RPD needs to be taken into account when discussing a patient’s prognosis and planning management.


Age-related macular degeneration (AMD) is phenotypically diverse, and a number of risk factors are associated with progression to sight-threatening, late-stage disease. It is important both clinically and scientifically to characterize the nature and impact of risk factors on progression to enable appropriate patient management and targeted clinical research.

Clinical classification systems, based on color fundus images, have enabled risk stratification based on the appearance of early AMD signs of drusen and pigmentary changes. Reticular pseudodrusen (RPD), seen clinically or on color images as a reticular pattern of small yellow-white lesions most often in the superior macula, also have been considered a high-risk sign for late AMD. New retinal imaging methods, in particular near-infrared reflectance (NIR) using a confocal scanning laser ophthalmoscope and spectral-domain optical coherence tomography (SD OCT), are much more sensitive at detecting RPD than clinical examination and have revealed a higher prevalence of AMD than previously assumed. To date, however, all studies assessing the impact of RPD on the progression of AMD lacked appropriate imaging and did not include both NIR and SD OCT, which have been shown to have the highest sensitivity in detecting RPD when used in combination.

The presence of choroidal neovascularization (CNV) in the first eye places individuals at high risk of late-stage disease developing in their fellow eye. This risk may be exacerbated considerably by the presence of RPD. Against this background, we assessed the impact of the presence of RPD on the progression to late-stage AMD in fellow eyes of patients with CNV in their first eye using NIR and SD OCT imaging as part of a very comprehensive retinal imaging protocol.

Methods
The prospective inclusion of participants into a study of neovascular AMD that allowed this retrospective analysis was

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approved by the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital and the institutional review board of the University of Utah and adhered to the tenets of the Declaration of Helsinki. All participants included in this study provided consent before participation.

Participants
Participants were recruited from the medical retina clinic at the Royal Victorian Eye and Ear Hospital at the University of Melbourne, Melbourne, Australia, and the John A. Moran Eye Center at the University of Utah, Salt Lake City, Utah, from 2010 through 2012. All consecutive subjects with newly diagnosed CNV secondary to AMD were recruited into longitudinal studies of neovascular AMD at both the Melbourne and Utah sites. They gave informed consent for their retinal images and medical records to be assessed. We retrospectively reviewed their data to address the question of the fellow eye by including only those participants with non–late-stage AMD in their fellow eye and follow-up for at least 1 year, unless late-stage AMD developed in the fellow eye in less than 1 year, in which case they were not excluded from analyses. Exclusion criteria for all participants based on the assessment of all images included the presence of late-stage AMD (including any geographic atrophy [GA] and CNV) or other retinal pathologic lesions against a background of mild retinal pigment hypereosin on NIR with corresponding hyperreflectance on SD OCT and NIR. Geographic atrophy was defined based on clinical examination and color photography with lesions larger than 175 μm and within 2 disc diameters of the fovea and confirmed on SD OCT and NIR.

Statistical Analyses
Univariate and multivariate survival analyses (Kaplan-Meyer and Cox) were performed to investigate the influence of baseline characteristics (including age, sex, presence of RPD, drusen, and pigmentary changes) on hazard rates of late-stage AMD. These were performed first combining all cases of late-stage AMD and then separately for the occurrence of CNV and GA, adjusting the level of significance according to the number of factors tested in the model. All analyses were performed with SPSS software version 19.0 (IBM, New York).

Results
A total of 200 participants (61% female) with unilateral CNV without late AMD in the fellow eye fitted the inclusion and none of the exclusion criteria at the 2 sites and were included in our analysis (Table 1). All participants underwent anti–vascular endothelial growth factor treatment for CNV. Participants had a mean age ± standard deviation of 77 ± 7 years. Overall, the prevalence of RPD in fellow eyes was 58%; 68% had drusen of 125 μm or more, and 36% had pigmentary changes. Twenty patients (10%) did not have any risk factors observed in the fellow eye, 44 patients (22%) had only either drusen of 125 μm or more or pigmentary abnormalities, 20 patients (10%) had both drusen of 125 μm or more and pigmentary abnormalities, and 34 patients (17%) had only RPD. Forty-one patients (20.5%) had presentation, and indocyanine green angiography and fundus autofluorescence were performed as clinically indicated.

End Points
All participants were followed up for a mean ± standard deviation of 2 ± 1.3 years (median, 2 years; range, 7.4 years), and the time to the development of either GA or CNV was determined. End-stage disease was classified as either GA or CNV depending on whichever late stage developed first. Choroidal neovascularization was defined based on clinical examination and was confirmed by SD OCT and fluorescein angiography. Geographic atrophy was defined based on clinical examination and color photography with lesions larger than 175 μm and within 2 disc diameters of the fovea and confirmed on SD OCT and NIR.
RPD with either drusen of 125 μm or more or pigmentary abnormalities, and another 41 patients (20.5%) had RPD with both drusen and pigmentary abnormalities.

After a mean follow-up of 2.3 years, 36% of fellow eyes progressed to CNV and 14% of fellow eyes progressed to GA in the overall sample. Persons in whom late-stage disease did not develop had the longest follow-up (2.6±1.9 years, compared with 2.4±1.5 years in GA [P = 1.000] and 1.9±1.2 years in CNV [P = 0.023]).

Persons with RPD and without RPD did not differ in age, sex, follow-up, or presence of drusen of 125 μm or more and pigmentary changes at baseline (Table 1). More persons with RPD, however, demonstrated late-stage AMD during follow-up (61% vs. 33.4%; P < 0.001), and most of this discrepancy was the result of a much higher occurrence of GA compared with persons with no RPD (22.4% vs. 2.4%; P < 0.001; Table 1).

Based on Kaplan-Meier survival analysis (Fig 1), the estimate for the mean time from presentation with a CNV in the first eye until onset of GA in the fellow eye of participants with RPD was shorter (4.54±0.38 years) compared with those without RPD (7.11±0.27 years; P < 0.001, log-rank test; Kaplan-Meyer survival plots in Fig 1). The difference in the estimate of mean time to development of CNV was not significantly different between the 2 groups (3.69±0.32 and 4.62±0.43 years, respectively; P = 0.355, log-rank test; Kaplan-Meyer survival plots in Fig 1).

Stratifying the development of late-stage AMD by number of macular risk factors (drusen ≥125 μm, pigmentary changes, and RPD), having just drusen and pigmentary changes or just RPD cause CNV and GA to occur earlier compared with having no risk factors. Having drusen, pigmentary changes, or both as well as having RPD, the highest risk of developing late-stage AMD (P < 0.001 for any late-stage AMD, P < 0.001 for GA, and P = 0.015 for CNV; Kaplan-Meier plots in Fig 2). No patients without any macular risk factors and 31% (25 of 82) of patients with all risk factors in GA. Four of 20 patients (20%) with no macular risk factors in the fellow eye CNV, and 40% (33 of 82) of patients with all risk factors CNV.

Figure 1. Kaplan-Meier plots for time until progression to (A) choroidal neovascularization (CNV) and (B) geographic atrophy (GA). Those with reticular pseudodrusen (RPD; black line) had a significantly shorter time to progression to GA compared with those without (grey line; P < 0.001). No difference was found for progression to CNV (P = 0.355).

Figure 2. Kaplan-Meier plots for time until progression to (A) late-stage age-related macular degeneration (AMD), (B) geographic atrophy (GA), and (C) choroidal neovascularization (CNV), stratified by number of risk factors (RFs; none, reticular pseudodrusen [RPD], and RPD plus drusen and/or pigment). For both CNV and GA, patients with all RFs (RPD plus drusen and/or pigment) progressed the fastest (P < 0.001 for any late-stage AMD, P < 0.001 for GA, and P = 0.015 for CNV). Note that in no patient with no RFs did GA develop, whereas in a number of patients with no RFs, CNV developed in the fellow eye during follow-up.
In multivariate Cox regression analysis, both drusen of 125 μm or more and pigmentary changes at baseline were significant risk factors for the development of CNV and GA (Table 2). However, RPD was a significant risk factor only for the development of GA and not for CNV (Table 2).

Discussion

In this sample, we found RPD to be an independent risk factor for GA development, but not CNV, in the fellow eye of patients being treated with anti–vascular endothelial growth factor therapy for CNV in the first eye. Both drusen of 125 μm or more and pigmentary changes at baseline were significant risk factors for the development of CNV and GA, with the additional presence of RPD exacerbating this risk for the development of both forms of late-stage AMD. Our findings have implications for monitoring and counseling high-risk patients with RPD, who will require close follow-up. Furthermore, being at high risk of GA developing in the fellow eye but having no signs of late AMD at baseline makes this group of great interest for future clinical trials of interventions to prevent or slow the development of GA.

In agreement with a number of previous studies, we found RPD to be a risk factor for the development of late-stage AMD, particularly GA, in our cohort of patients with CNV in their first eye, that is, a high risk for progression in the fellow eye. A French study demonstrated RPD to be a risk factor for CNV as well as GA in a very similar group of patients with CNV in their first eye but used only blue reflectance photography and fluorescein angiography to detect RPD. However, a combination of SD OCT and NIR has been shown to have the highest sensitivity in detecting RPD and thus was used in our study. In fact, blue reflectance photography has been shown to have a low interobserver agreement in detecting RPD compared with NIR. Therefore, participants in that study may have been misclassified with respect to their RPD status. This is highlighted by a previous study that investigated the prevalence of RPD in a group of patients with newly diagnosed CNV. Reticular pseudodrusen were determined on the basis of fluorescein angiography and blue reflectance and red-free photography, and neither OCT nor NIR imaging were performed. The proportion of patients found to have RPD was considerably lower (24%) compared with studies using SD OCT (35%–38%), NIR (62%), or NIR combined with SD OCT (58% in our sample) in very similar samples of high-risk patients. Against this background, we are confident that the imaging used in this study reliably detected RPD because the sensitivity and specificity of combining NIR and SD OCT has been shown to be superior to that of other imaging techniques.

A number of risk factors for the development of late-stage AMD in the second eye have been described. Presence of drusen of 125 μm or more and pigmentary changes, in association with late-stage disease in the fellow eye, confer a risk of progression of approximately 50% over 5 years, as demonstrated by the Age-Related Eye Disease Study. In a systematic review of all available studies, the cumulative incidence of late-stage AMD in fellow eyes of persons with unilateral CNV was found to be 11% to 12% at 1 to 2 years, 21% at 3 years, and 27% at 4 years. The overall rate of progression to late-stage AMD in patients with RPD observed in our study (61% over 2.5 years) is similar to the only other study assessing progression to late-stage AMD in patients with RPD and unilateral CNV (56% over 3 years). Both are considerably higher than the overall progression rates reported for pooled samples including persons with and without RPD and highlights once more the high risk for the development of late-stage AMD conferred by RPD. This risk seems to be in addition to the risk conveyed by the conventional macular risk factors of drusen and pigmentary changes as demonstrated by our Kaplan-Meier plots. However, because of sample size restrictions and censored follow-up, RPD was not confirmed as an independent risk factor for CNV development in fellow eyes in subsequent Cox survival analyses. Given the importance of establishing risk factors for the progression to late-stage AMD, future studies should aim to clarify these associations.

To our knowledge, this is the first study assessing the influence of RPD on progression of AMD in high-risk patients using a combination of SD OCT and NIR. Limitations of this study are its moderate size and limited follow-up and the selection bias inherent in all clinical case series.

Table 2. Cox Regression Analysis Results for Hazard Rates of Late-Stage Age-Related Macular Degeneration, Controlling for Age and Sex

<table>
<thead>
<tr>
<th>Late Age-Related Macular Degeneration</th>
<th>Risk Factors</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNV</td>
<td>RPD</td>
<td>1.19</td>
<td>0.72–1.94</td>
<td>0.500</td>
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<td></td>
<td>Drusen ≥125 μm</td>
<td>1.96</td>
<td>1.14–3.36</td>
<td>0.015</td>
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<td>Pigmentary changes</td>
<td>2.49</td>
<td>1.51–4.10</td>
<td>&lt;0.001</td>
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<tr>
<td>GA</td>
<td>RPD</td>
<td>4.93</td>
<td>1.26–22.93</td>
<td>0.042</td>
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<td>Drusen ≥125 μm</td>
<td>11.73</td>
<td>1.47–93.81</td>
<td>&lt;0.020</td>
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<td>Pigmentary changes</td>
<td>5.75</td>
<td>2.29–15.84</td>
<td>0.001</td>
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<tr>
<td>CNV or GA</td>
<td>RPD</td>
<td>1.20</td>
<td>0.76–1.89</td>
<td>0.433</td>
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<td></td>
<td>Drusen ≥125 μm</td>
<td>2.08</td>
<td>1.25–3.49</td>
<td>0.008</td>
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<td></td>
<td>Pigmentary changes</td>
<td>2.35</td>
<td>1.64–3.96</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CNV = choroidal neovascularization; GA = geographic atrophy; RPD = reticular pseudodrusen.
recruiting patients prospectively or retrospectively at tertiary eye hospitals. However, it is a representative group of patients with neovascular AMD seeking treatment at 2 medical retina departments and who are at a high risk of bilateral visual loss when late-stage disease develops in the second eye. Results can be generalized to patients seen at these specialist clinics and the information can be extrapolated carefully. Further strengths of this study are its comprehensive and highly appropriate retinal imaging. Based on a number of previous studies, we are confident that we detected RPD with the highest possible accuracy. Similarly, the regular—up to monthly—follow-up inclusive of NIR and SD OCT imaging allowed for a very precise definition of the 2 end points, CNV and GA, as well as an accurate timing of its occurrence.

In conclusion, we demonstrated RPD to be an independent risk factor for GA in high-risk AMD, in addition to other risk factors such as drusen of more than 125 μm and pigmentary changes. With the ubiquity of OCT, which usually includes infrared imaging, clinicians should keep RPD at the forefront of their minds when discussing patients’ prognosis and the risk of late-stage disease developing in fellow second eyes.

References


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; CNV = choroidal neovascularization; GA = geographic atrophy; HR = hazard ratio; NIR = near-infrared reflectance; RPD = reticular pseudodrusen; SD OCT = spectral-domain optical coherence tomography.

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